Indobufen
A review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in Cerebral, Peripheral and Coronary Vascular Disease

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Contents

Summary

1. Pharmacodynamic Properties
   1.1 Effects of Indobufen on Platelet Function
      1.1.1 Platelet Thromboxane Synthesis
      1.1.2 Platelet Aggregation
      1.1.3 Platelet Release Reaction
      1.1.4 Platelet Adhesion
   1.2 Effects on Blood Coagulation and Erythrocyte Deformability
   1.3 Effects on Microcirculatory Parameters
   1.4 In Vivo Effects in Experimental Models of Thrombosis

2. Pharmacokinetic Properties
   2.1 Absorption
   2.2 Distribution and Elimination
   2.3 Influence of Age and Renal Disease on Pharmacokinetics

3. Therapeutic Use
   3.1 Treatment of Occlusive Vascular Disease
   3.2 Prophylactic Use in Occlusive Vascular Disease
      3.2.1 Arterial Bypass Graft Surgery, Carotid Endarterectomy and Coronary Angioplasty
      3.2.2 Transient Ischaemic Attack and Stroke
      3.2.3 Deep Vein Thrombosis
      3.2.4 Haemodialysis
      3.2.5 Migraine

4. Tolerability
5. Drug Interactions
6. Dosage and Administration
7. Place of Indobufen in Therapy
**Summary**

**Synopsis**

Indobufen is an inhibitor of platelet aggregation which acts by reversibly inhibiting the platelet cyclo-oxygenase enzyme. Improvements in walking distances and microcirculatory parameters have been achieved during therapy with indobufen in patients with peripheral vascular disease and intermittent claudication. Indobufen has been shown to be as effective as aspirin plus dipyridamole in preventing the reocclusion of coronary and femoro-popliteal artery bypass grafts and has been shown to significantly reduce platelet deposition on haemodialysis membranes. Initial studies have also indicated that indobufen may have a prophylactic effect on the incidence of secondary thrombotic events following transient ischaemic attack or mild stroke and may be effective in the prophylaxis of migraine.

Indobufen is well tolerated following oral administration and has been associated with a low incidence of adverse effects rarely requiring withdrawal of treatment.

Thus, available evidence indicates that indobufen may be an effective alternative to aspirin for the treatment of cerebral, peripheral and coronary vascular diseases with the advantage of a lower incidence of gastrointestinal effects compared to high dose aspirin, rendering indobufen more suitable for longer term therapy.

**Pharmacodynamic Properties**

Indobufen is an isoindolinyl phenyl-butyric acid derivative that produces reversible inhibition of platelet aggregation *in vitro* and *ex vivo*. Platelet cyclo-oxygenase is reversibly inhibited by indobufen and this results in decreased production of thromboxane B₂, a potent activator of platelet aggregation. The drug inhibits the second wave of aggregation induced by adenosine diphosphate (ADP), epinephrine (adrenaline) and platelet activating factor (PAF) in platelets from healthy volunteers and from patients with occlusive vascular disease, and has a dose-dependent inhibitory effect on collagen- and arachidonic acid-induced aggregation. A maximal inhibitory effect on agonist-induced platelet aggregation is observed 2 hours after a single oral dose of indobufen 200mg. This inhibition is still significant (90%) after 12 hours and is reversible within 24 hours. Indobufen therapy (200mg twice daily) significantly inhibits spontaneous platelet aggregation *ex vivo* compared with placebo in platelets from atherosclerotic patients, and this is evident 2 to 8 hours after administration.

Other effects include a reduction in the platelet levels of adenosine triphosphate (ATP), serotonin (5-hydroxytryptamine), platelet factor 3 (PF3), PF4 and β-thromboglobulin (BTG), decreased platelet adhesiveness in platelets from healthy volunteers and from atherosclerotic patients and an improvement in red blood cell deformability in patients with occlusive vascular disease. Bleeding time is prolonged following indobufen administration, with a maximal effect 2 hours after administration; however, this increase is not clinically relevant and values remain within the upper normal limit at all times.

Improvements in microcirculatory parameters, including resting and standing skin blood flow and the venoarteriolar reflex have been found in patients with intermittent claudication and diabetes following indobufen therapy.

Indobufen demonstrated antithrombotic activity *in vivo* in animals against the lethal thrombotic effects of epinephrine and collagen and prevented graft occlusion following vascular surgery.

**Pharmacokinetic Properties**

Indobufen is readily absorbed following oral administration with peak plasma concentrations of 12.5 to 14.9 mg/L being attained at 2 hours after a single dose of 100mg. Steady-state peak plasma concentrations of 16.7 and 29.2 mg/L are achieved after oral administration of indobufen 100 and 200mg twice daily for 7.5 and 5 days, respectively. Indobufen is highly bound to plasma proteins (> 99%) and this is reflected in its low apparent volume of distribution (13 to 15L). The elimination half-life of indobufen is within the range of 6 to 8 hours in healthy volunteers and about 75% of the dose is recovered in urine within 48 hours of administration. About 13% of the dose is excreted unchanged and the remainder as a glucuronic acid conjugate. In the elderly
and in patients with renal insufficiency, the area under the plasma concentration-time curve and plasma elimination half-life of indobufen are significantly prolonged and dose reduction is required.

Therapeutic Use

Indobufen 200mg twice daily improves walking distances in patients with intermittent claudication. Walking distances were significantly improved in patients receiving indobufen compared with patients receiving placebo ($p < 0.05$) within 10 days of starting therapy, and continued to improve during 6 months of indobufen therapy. In one nonrandomised comparative study, indobufen 200mg twice daily was found to cause a more marked improvement in pain-free walking distance and total walking distance than aspirin 500mg twice daily after 1 year.

Several studies evaluated the efficacy of indobufen in improving graft patency following surgery. Indobufen 200mg twice daily was as effective as aspirin 975mg + dipyridamole 225mg daily in reducing the incidence of coronary artery bypass graft (CABG) reocclusion, which occurred with a frequency of 34% in both treatment groups after 1 year of therapy. Platelet accumulation and lesion formation following carotid endarterectomy were reduced in patients receiving indobufen 200mg twice daily compared with placebo after a 6-month treatment period.

Preliminary investigation of the use of indobufen in the secondary prevention of occlusive vascular events has indicated a potential prophylactic benefit of indobufen in patients following transient ischaemic attack, mild stroke or acute myocardial infarction. In one study the incidence of secondary cardiovascular events in patients treated with indobufen 100mg twice daily was 5% compared to 15% in the placebo group after 26 months.

An initial study has indicated that indobufen may also have a prophylactic effect in patients with classic or common migraine.

Clinical trials evaluating the efficacy of indobufen in reducing platelet aggregation on haemodialysis membranes have found a significant reduction in membrane occlusion after administration of indobufen 200mg twice daily for 7 days (30%) compared to placebo (51.5%) suggesting that indobufen therapy improves the efficiency of haemodialysis.

Tolerability

Indobufen 200mg twice daily has been well tolerated in patients with vascular disease, with adverse effects occurring in approximately 3 to 9% of patients; discontinuation of therapy has rarely been necessary (in approximately 1% of those treated). The majority of adverse effects reported during treatment are gastrointestinal and include dyspepsia, abdominal pain, constipation, nausea and vomiting. Haemostasis and coagulation disorders and skin and central nervous system (CNS) disorders have been reported in a small number of patients. In comparative studies, the incidence of adverse effects was lower in patients receiving indobufen 200mg twice daily (9%) compared with aspirin 975mg daily plus dipyridamole 225mg daily (18%).

Dosage and Administration

The oral daily dose of indobufen is generally 200 to 400mg, given in 2 divided doses after meals. Dosage reductions are necessary in the elderly and in patients with renal insufficiency.
Indobufen or \([p-(1\text{-oxo-2-isoindolinyl})\text{-phenyl}]\text{butyric acid}\) has been found to have platelet antiaggregatory effects both \textit{in vitro} and \textit{ex vivo} and has proven effective in clinical trials for the treatment and prophylaxis of coronary, cerebral and peripheral vascular diseases.

\section*{1. Pharmacodynamic Properties}

\subsection*{1.1 Effects of Indobufen on Platelet Function}

\subsection*{1.1.1 Platelet Thromboxane Synthesis}

Extrinsic factors such as collagen, thrombin and epinephrine (adrenaline), which are released at sites of vascular damage, trigger platelet activation and aggregation. Activated platelets synthesise and release compounds such as ADP (adenosine diphosphate), serotonin (5-hydroxytryptamine) and platelet derived growth factor (PDGF) which can potentiate platelet aggregation, synthesis and release. Stimulation of arachidonic acid metabolism in platelets initiated by phospholipase A2 is an important pathway in the mechanism of platelet activation. Thromboxane B2 (TXB2) is a metabolic product of arachidonic acid which has powerful platelet aggregating activity and also acts as a vasoconstrictor.

Indobufen inhibits the stimulatory effect of agonists on platelets by reversibly inhibiting arachidonic acid metabolism through inhibition of the platelet cyclooxygenase enzyme (fig. 2), which is important in the production of TXB2, a stable derivative of thromboxane A2 (TXA2). Indobufen is an optically active compound with the S-enantiomer responsible for the majority of the platelet inhibitory activity; however, studies have found no significant difference in cyclooxygenase inhibitory potency between the racemate and S-indobufen (Cerletti et al. 1990; De Caterina et al. 1992; Patrignani et al. 1990).

\textit{In vitro} and \textit{ex vivo} analysis of the effects of indobufen on intraplatelet \textsuperscript{14}C\textendash arachidonic acid metabolism has been examined using high performance liquid chromatography (HPLC). Pinto et al. (1987) reported a linear relationship between TXB2 inhibition and log drug concentration (0.015 to 60 \(\mu\text{mol/L}) in platelet-rich plasma from healthy volunteers. Indobufen caused inhibition of TXB2 production at very low concentrations, with 50\% inhibition occurring at 0.85 \(\mu\text{mol/L} and almost complete inhibition at 34 \mu\text{mol/L}. Oral administration of indobufen (200mg twice daily for 3 days) to healthy volunteers was also found to significantly inhibit platelet TXB2 production induced by thrombin. Maximal inhibition occurred 2 hours after drug administration and was still pronounced (95\%) 12 hours after the last dose (Pinto et al. 1987).

Oral indobufen 200mg causes significant \textit{ex vivo} inhibition of platelet TXB2 production induced by a number of different agonists in healthy volunteers (table I). Indobufen (10 \(\mu\text{mol/L}) had a comparable inhibitory effect \textit{in vitro} on platelet TXB2 production induced by ADP, epinephrine and

\begin{figure}
\centering
\includegraphics[width=\textwidth]{indobufen_diagram}
\caption{Structural formula of indobufen (2-[p-(1-oxo-2-isoin­
dolinyl)-phenyl] butyric acid); * = chiral centre.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{thromboxane_diagram}
\caption{Locus of action of indobufen in pathways of platelet arachidonic acid metabolism. Abbreviations: PG = prosta­
glandin; TX = thromboxane.}
\end{figure}
Indobufen: A Review

Table I. Inhibitory effects of indobufen ex vivo (200mg orally) and in vitro (10 µmol/L) on agonist-stimulated thromboxane B2 (TXB2) production in platelets from healthy volunteers (adapted from Cattaneo et al. 1987)

<table>
<thead>
<tr>
<th>Aggregating agent</th>
<th>Inhibition of TXB2 production (% of pretreatment level)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ex vivo</td>
</tr>
<tr>
<td>ADP 4 µmol/L</td>
<td>2.7</td>
</tr>
<tr>
<td>Epinephrine 10 µmol/L</td>
<td>0.1</td>
</tr>
<tr>
<td>PAF 0.2 µmol/L</td>
<td>1.2</td>
</tr>
<tr>
<td>2.0 µmol/L</td>
<td>0.9</td>
</tr>
<tr>
<td>Collagen 2 mg/L</td>
<td>0.1</td>
</tr>
<tr>
<td>4 mg/L</td>
<td>1.2</td>
</tr>
<tr>
<td>Arachidonic acid 1 mmol/L</td>
<td>2.5</td>
</tr>
<tr>
<td>2 mmol/L</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADP = adenosine diphosphate; PAF = platelet activating factor.

Platelet activating factor (PAF). In both studies, inhibition of TXB2 production induced by 2 mmol/L arachidonic acid was incomplete, and in the in vitro study 10 µmol/L indobufen did not cause complete inhibition of collagen-induced TXB2 production. A concentration of 100 µmol/L indobufen was required to inhibit the induction of TXB2 by collagen (2 mg/L) by 95%.

The findings that indobufen dose-dependently inhibits intracellular calcium mobilisation and inhibits inositol trisphosphate formation in collagen-stimulated platelets (Sumi et al. 1990) are also consistent with an inhibitory effect of the drug on TXB2 formation through inhibition of platelet cyclo-oxygenase.

The ex vivo effect of indobufen on platelet TXB2 production in patients with vascular disease has been investigated (Davi et al. 1988; Mannucci et al. 1987; Rebuzzi et al. 1990). The results of these studies are summarised in table II. TXB2 production during whole blood clotting and in platelet rich plasma from patients with ischaemic heart disease was almost completely inhibited 2 hours after a single oral dose of indobufen 200mg, and this inhibition was still pronounced at 12 hours postdose (89%) [Davi et al. 1988]. Inhibition was significantly attenuated (47%) after 24 hours, indicating that the effect of indobufen on cyclo-oxygenase activity is reversible. Similar results were reported in platelets from patients at high risk of developing atherosclerosis (Mannucci et al. 1987). Collagen-induced platelet TXB2 production was inhibited by more than 90% 2 hours after single oral doses of indobufen (200 or 400mg) and inhibitory activity was diminished but still significant 24 hours after indobufen administration (47% inhibition after 200mg and 70% inhibition after 400mg).

Oral indobufen therapy (100 or 200mg twice daily for 1 week) starting 3 to 10 days after the onset of acute myocardial infarction (n = 12) inhibited platelet TXB2 production by more than 90% 2 hours after the first dose, and production remained depressed throughout the 12 hour duration of the study (Rebuzzi et al. 1990).

1.1.2 Platelet Aggregation

Indobufen is an effective inhibitor of platelet aggregation both in vitro and ex vivo in healthy volunteers and patients with ischaemic heart disease. A significant correlation between plasma drug concentrations and antiaggregant activity ex vivo has been observed, with a minimum plasma concentration of 4 mg/L required to ensure inhibition of aggregation (Tamassia et al. 1979).

The results of studies investigating the ex vivo inhibitory effect of oral indobufen on platelet aggregation are reported in table III. Indobufen (200mg) significantly inhibits the secondary wave of aggregation induced by ADP, epinephrine and PAF but has no effect on the primary wave of aggregation induced by these agonists, indicating that it does not interfere with their specific pathways of platelet activation (Cattaneo et al. 1987; Davi et al. 1988). Inhibition of collagen- and arachidonic acid-induced aggregation was dose dependent and indobufen had no effect on the irreversible aggregation induced by higher concentrations of PAF (2 µmol/L).

Maximal ex vivo inhibition of ADP- and collagen-induced platelet aggregation was evident 2 hours after indobufen administration and this inhibition was reversible, with platelet aggregation...
returning to baseline within 24 hours of administration of a single 200mg dose (Carrieri & Orefice 1984; Crow et al. 1985; Mannucci et al. 1987; Pogliani et al. 1981a; Visona et al. 1983; Table III). Inhibition of collagen-induced aggregation was still significant, however, after 24 hours in patients who received a 300 or 400mg dose of indobufen (Mannucci et al. 1987; Vinazzer & Fuccella 1980). Indobufen has a similar inhibitory effect on platelet aggregation following single- and multiple-dose administration (Crow et al. 1985; Mannucci et al. 1987).

Platelets from patients with atherosclerotic disease and type IIA hypercholesterolaemia exhibit enhanced aggregability (Nenci et al. 1982; Tremoli et al. 1981; Visona et al. 1983). In a placebo-controlled crossover study involving 8 patients with type IIA hypercholesterolaemia and 8 healthy volunteers, platelet aggregation in response to threshold concentrations of epinephrine and arachidonic acid was greater in patients with type IIA hypercholesterolaemia; however, indobufen (200mg twice daily for 3 days) completely suppressed platelet aggregation in both patients and healthy controls (Tremoli et al. 1981). Lower concentrations of aggregating agents were required to overcome the inhibitory effect of indobufen on platelets from type IIA patients compared with healthy controls.

Nenci et al. (1982) have used Breddin’s platelet aggregation test to study the effects of indobufen on the spontaneous aggregation of platelets in their normal environment. Administration of indobufen (100 or 200mg twice daily) resulted in prompt normalisation of the enhanced platelet aggregation found in 12 patients with atherosclerotic disease. Furthermore, 50% of the patients maintained a normal level of spontaneous platelet aggregation 4 days after discontinuing treatment; a return to baseline activity levels was demonstrable after 8 days.

A similar inhibitory effect of indobufen on spontaneous platelet aggregation in patients with atherosclerosis has been found using the platelet aggregation filtration pressure (PAFP) test (Visona et al. 1983). In this study a single oral or intravenous dose of indobufen 200mg markedly reduced platelet aggregation compared with placebo after 2, 4 and 8 hours, with values increasing after 24 hours, and there was no significant difference in potency between the 2 routes of administration.

Platelet sensitivity to aggregating agents increases during exercise in patients with stable angina. When compared with placebo in a double-blind crossover study, a single oral dose of indobufen 200mg markedly inhibited ADP- and collagen-induced platelet aggregation (Pogliani et al. 1981b). Evening administration of indobufen 200mg inhibited the increase in platelet sensitivity to the agonists ADP and collagen which frequently occurs between 6am and 9am in both healthy volunteers and in patients with ischaemic heart disease (Craveri et al. 1989).

### Table II. Ex vivo inhibition of platelet arachidonic acid metabolism determined at various times following oral indobufen administration to patients with vascular disease or hyperlipidaemia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Indobufen dose (mg)</th>
<th>Duration of treatment</th>
<th>Inhibition of TXB₂ production (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davi et al. (1988)</td>
<td>20 IHD</td>
<td>200 bid</td>
<td>4 weeks</td>
<td>98 89 47</td>
</tr>
<tr>
<td>Mannucci et al. (1987)</td>
<td>16 Ath risk</td>
<td>200 Single dose 400 &gt; 90 &gt; 90 70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rebuzzi et al. (1990)</td>
<td>12 AMI</td>
<td>200 bid</td>
<td>1 week</td>
<td>&gt; 90 &gt; 90</td>
</tr>
</tbody>
</table>

Abbreviations: AMI = acute myocardial infarction; Ath risk = atherosclerotic risk; bid = twice daily; h = hours; IHD = ischaemic heart disease.
Indobufen administration has been associated with a reduction in levels of circulating platelet aggregates in patients with transient cerebral ischaemia (Carrieri et al. 1983). Levels were significantly reduced within 2 hours of indobufen administration (200mg) and remained significantly depressed after 5 days of treatment.

1.1.3 Platelet Release Reaction
Platelets contain dense and alpha secretory granules, the contents of which are released during platelet aggregation. Alpha granules contain fibrinogen, fibronectin, von Willebrand factor, platelet factor 4 (PF4) and beta-thromboglobulin (BTG), and dense granules contain ADP, serotonin, calcium and phosphate salts. The release of granule contents is an important factor in platelet activation as the majority of these substances are involved in platelet adhesion and aggregation at sites of vascular damage. Indobufen has an inhibitory effect on the platelet release reaction in both in vitro and ex vivo studies of human platelets.

ATP release in response to ADP, epinephrine and PAF was inhibited in platelets from healthy volunteers following incubation with indobufen (10 μmol/L) in vitro (Cattaneo et al. 1987); furthermore, agonist-induced ATP release was inhibited ex vivo 2 hours after oral administration of indobufen 200mg. Serotonin release from platelets after exercise in patients with angina is also inhibited following indobufen administration (Pogliani et al. 1983).

In a study which used radioimmunoassay (RIA) to investigate platelet function in 6 healthy volunteers, Crow et al. (1985) observed a decrease in plasma PF3 levels 2 and 4 hours after a single dose of indobufen 200mg and 12 hours after multiple-dose administration of indobufen (200mg twice

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Indobufen dose (mg)</th>
<th>Duration of treatment</th>
<th>Agonist</th>
<th>Inhibition of platelet aggregation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattaneo et al. (1987)</td>
<td>8 Healthy volunteers</td>
<td>200</td>
<td>Single dose</td>
<td>ADP 4 μmol/L</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adrenaline 10 μmol/L</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PAF 0.2 μmol/L</td>
<td>50</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td>PAF 0.4 μmol/L</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>AA 1 mmol/L</td>
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<td></td>
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<td></td>
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<td>Collagen 2 mg/L</td>
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<td></td>
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<td>Collagen 4 mg/L</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>200 bid</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Davi et al. (1988)</td>
<td>8 Healthy volunteers</td>
<td>200 bid</td>
<td>7 days</td>
<td>ADP 5 μmol/L</td>
<td>32</td>
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<td>PAF 0.5 μmol/L</td>
<td>38</td>
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<td>AA 0.4 μmol/L</td>
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<td>Collagen 2 mg/L</td>
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<td></td>
<td>ADP 3 μmol/L</td>
<td>28</td>
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<td>PAF 0.5 μmol/L</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Collagen 2 mg/ml</td>
<td>44</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AA 0.4 μmol/L</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Spontaneous</td>
<td>32</td>
</tr>
<tr>
<td>Visona et al. (1983)</td>
<td>12 Ath</td>
<td>200</td>
<td>Single dose</td>
<td>ADP 4 μmol/L</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adrenaline 10 μmol/L</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PAF 0.2 μmol/L</td>
<td>15</td>
</tr>
</tbody>
</table>

**Abbreviations:** AA = arachidonic acid; Ath = patients with atherosclerosis; ADP = adenosine diphosphate; bid = twice daily; IHD = patients with ischaemic heart disease; PAF = platelet activating factor.
daily for 6 days). PF4 and BTG plasma levels, determined by RIA, were both significantly reduced during indobufen therapy in patients with transient cerebral ischaemia (Carrieri & Orefice 1984; Orefice et al. 1984), and significant inhibition of PF4 release and PF3 availability has also been reported in patients with vascular disease following single (300mg) or repeated dose (200mg twice daily for 10 days) indobufen administration (Ciavarella et al. 1981; Vinazzer & Fuccella 1980).

1.1.4 Platelet Adhesion

Platelet adhesion to the subendothelium of the vessel wall is an important step in the mechanism of platelet aggregation. Although initial in vitro studies found no effect of indobufen on platelet adhesiveness to glass microphores, subsequent ex vivo studies have shown indobufen treatment to significantly decrease platelet adhesiveness (Carrieri & Orefice 1984; Moia et al. 1988; unpublished data on file, Farmitalia Carlo Erba). This was evident both 2 hours after a single oral dose of indobufen (100 to 200mg) and after 5 days treatment in healthy volunteers and in patients with transient cerebral ischaemia. Nenci et al. (1982) have also reported a decrease in platelet adhesion in patients with atherosclerotic disease, although this effect reached statistical significance only at the fourth day of treatment with indobufen 200mg twice daily. Crow et al. (1985) failed to detect any significant difference in platelet adhesion 2 and 4 hours after a single oral dose of indobufen 200mg, and after multiple doses, in healthy volunteers. Platelet adhesion to siliconised glass and bovine extracellular matrix was significantly inhibited 1 hour after a single intravenous injection of indobufen 200mg in patients with peripheral obliterative disease (Belcaro et al. 1990a,b; Signorini et al. 1988). Signorini et al. (1988) found a significant difference (p < 0.01) in skin blood flow between placebo and indobufen groups, with the indobufen group showing an improvement and the placebo group showing no change or a deterioration. Indobufen (200mg twice daily) significantly (p < 0.05) increased mean resting skin blood flow (0.55 ml/min) compared with basal levels (0.41 ml/min) after 10 days and a significant improvement (p < 0.05) in the venoarteriolar reflex was also found after 10 days' therapy (Belcaro 1990b). The venoarteriolar reflex was fur-
ther improved after combined treatment with indobufen and defibrotide.

The effect of indobufen on microcirculatory parameters in diabetic patients has been investigated in a preliminary study (Belcaro et al. 1990c). Twice daily administration of indobufen 200mg for 1 year to 82 patients with diabetic microangiopathy resulted in a slight, nonsignificant improvement in resting and standing skin blood flow and a significant improvement (p < 0.05) in the veno-arteriolar reflex compared with baseline values (18.2% decrease in flow on standing with indobufen vs 16.5% at baseline). These parameters deteriorated in untreated patients and there was a significant (p < 0.05) difference between the treated and untreated patients.

1.4 In Vivo Effects in Experimental Models of Thrombosis

Animal model systems have proved useful in the analysis of the antithrombotic properties of indobufen in vivo. Using a mouse antithrombotic assay, Di Minno and Silver (1983) have evaluated and compared the properties of several agents in vivo. In male Swiss-Webster mice, a combination of alcohol (ethanol) 2 g/kg and indobufen 0.5 mg/kg provided complete protection against the lethal thrombotic effects of a mixture of collagen and epinephrine. Ethanol and indomethacin also provided complete protection, whereas a combination of ethanol and aspirin provided 84% protection.

Animal models have also been used to assess the ability of indobufen to prevent thrombosis following vascular surgery. Carrieri et al. (1987) investigated the antithrombotic effect of indobufen following the formation of an end-to-side anastomosis between the left and right common carotid arteries in rats. Total occlusion of the anastomosis was found in 8 of 15 untreated rats, whereas indobufen completely inhibited thrombus formation in 14 of 15 treated rats. Administration of indobufen 200mg twice daily for 2 days prior to surgery was significantly more effective (p < 0.05) than placebo in reducing autologous platelet deposition in femoral artery grafts in dogs, and graft occlusion was prevented for up to 28 days after implantation (Lane et al. 1986).

Using an artificial circulation and blood from healthy volunteers who had received indobufen (200mg twice daily for 1 week), Sheehan et al. (1988) studied the in vitro effect of indobufen on the thrombogenic potential of a ‘Dacron’ prosthesis. These investigators observed significant inhibition of platelet aggregation in blood from indobufen-treated patients compared with blood flow from a placebo group, suggesting that indobufen may be an effective antiplatelet agent for use following bypass surgery involving these prostheses.

2. Pharmacokinetic Properties

The pharmacokinetic profile of indobufen has been investigated following both oral and intravenous administration in healthy volunteers. The effects of age and renal disease on the bioavailability and excretion of the drug have also been studied. Concentrations of unchanged indobufen in plasma, and of unchanged and total indobufen in urine, were determined by high-performance liquid chromatography (HPLC) or gas-liquid chromatography (GLC). HPLC accurately measures indobufen concentrations above 4.4 mg/L in plasma and GLC accurately measures concentrations above 0.3 mg/L in plasma and above 2.5 mg/L in urine (coefficient of variation 2%).

A summary of results from studies investigating the pharmacokinetics of indobufen following single oral administration to healthy volunteers is presented in table IV.

2.1 Absorption

Indobufen is rapidly and almost completely absorbed following oral administration, and peak plasma concentrations (C_{max}) are reached within 2 hours (t_{max}). Following administration of a range of single doses between 100 and 400mg, maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) values were dose related (Fuccella et al. 1979; Tamassia et al. 1979; unpublished data on file, Famitalia
### Table IV. Pharmacokinetics of indobufen in healthy young volunteers following single oral dose administration

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of volunteers</th>
<th>Dose (mg)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;0-oo&lt;/sub&gt; mg/L· h</th>
<th>t&lt;sub&gt;1/2p&lt;/sub&gt; (h)</th>
<th>U&lt;sub&gt;un&lt;/sub&gt; (mg)</th>
<th>U&lt;sub&gt;tot&lt;/sub&gt; (mg)</th>
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</thead>
<tbody>
<tr>
<td>Fuccella et al. (1979)</td>
<td>6</td>
<td>100</td>
<td>12.5</td>
<td>1.8</td>
<td>157.4</td>
<td>6.7</td>
<td>11.39</td>
<td>67.27</td>
</tr>
<tr>
<td>Savazzi et al. (1984)</td>
<td>6</td>
<td>200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamassia et al. (1979)</td>
<td>6</td>
<td>100</td>
<td>14.6</td>
<td>1.5</td>
<td>74.8</td>
<td>7.6</td>
<td>13.31</td>
<td>71.25</td>
</tr>
<tr>
<td>Unpublished data on file,</td>
<td>9</td>
<td>100</td>
<td>14.9</td>
<td>1.3</td>
<td>81.5</td>
<td>7.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmitalia Carlo Erba</td>
<td></td>
<td>200</td>
<td>26.5</td>
<td>1.2</td>
<td>178.5</td>
<td>7.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>400</td>
<td>48.2</td>
<td>1.8</td>
<td>360.5</td>
<td>8.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AUC<sub>0-oo</sub> = area under the plasma concentration-time curve extrapolated to infinity; C<sub>max</sub> = maximum plasma concentration; t<sub>max</sub> = time to achieve C<sub>max</sub>; t<sub>1/2p</sub> = terminal phase elimination half-life; U<sub>un</sub> = urinary excretion of unchanged drug; U<sub>tot</sub> = urinary excretion of total drug.

Carlo Erba). T<sub>max</sub> was not modified by increasing doses of up to 400mg and ranged from 1.2 to 1.8h. After a single oral dose of indobufen 100mg, C<sub>max</sub> ranged from 12.5 to 14.9 mg/L. After 15 consecutive doses of indobufen 100mg twice daily the mean C<sub>max</sub> was 16.7 mg/L and was 29.2 mg/L after 10 consecutive doses of indobufen 200mg twice daily (Savazzi et al. 1986; Tamassia et al. 1979).

Intake of food prior to indobufen administration (100mg) caused a slight but significant (p < 0.01) decrease in the bioavailability of the drug in 6 healthy volunteers (Tamassia et al. 1979). Mean C<sub>max</sub> values were reduced from 14.61 to 10.24 mg/L in the presence of food, and AUC values decreased from 74.78 to 64.67 mg/L· h. Absorption of indobufen tablets, determined by urinary excretion of unchanged and total indobufen, was not affected by the presence of food. This reduction in bioavailability does not appear to have any appreciable effect on the pharmacological activity of indobufen (Tamassia et al. 1979).

2.2 Distribution and Elimination

Indobufen has a low apparent volume of distribution in humans which is consistent with the high affinity of the drug for plasma proteins (>99% bound to protein). The apparent volume of distribution ranged from 13 to 15L with a mean value of 14.5L in 5 healthy volunteers following a single oral dose of indobufen 100mg (Fuccella et al. 1979).

The curve describing disappearance of indobufen from plasma is biphasic; the terminal phase elimination half-life is 6 to 8 hours in healthy volunteers (table IV). 70 to 80% of the dose of indobufen is recovered in urine within 48 hours of administration, with the majority excreted via the kidney as glucuronic acid conjugates and a small percentage (11 to 13%) excreted as unchanged drug (Fuccella et al. 1979; Tamassia et al. 1979). No significant difference has been reported in excretion rates following oral and intravenous administration, and food intake does not affect renal clearance of indobufen (Fuccella et al. 1979; Tamassia et al. 1979). The plasma clearance of the drug was similar following single or repeated administration both in healthy volunteers and in elderly patients with vascular diseases (Savazzi et al 1986; Tamassia et al. 1979). No induction or inhibition of metabolism of indobufen has been reported.

2.3 Influence of Age and Renal Disease on Pharmacokinetics

Savazzi et al. (1984) studied indobufen elimination in 11 patients with renal failure in comparison with 6 healthy volunteers. Elimination of indobufen was sensitive to the degree of renal insufficiency. The plasma clearance of the drug in healthy individuals (creatinine clearance >100 ml/min) was 22.3 ml/min and the plasma elimination half-life was 6.7 hours. In patients with moderate-to-severe renal impairment (creatinine clearance < 20 ml/min), plasma clearance was 7.1 ml/min and
the plasma elimination half-life was increased to 33.1 hours. Thus, dosage reduction is necessary to prevent excessive drug accumulation in these patients (see section 6).

The pharmacokinetics of indobufen were studied in 18 elderly patients (aged between 54 and 81 years) and compared with 18 young healthy volunteers following single (200mg) and repeated (200mg twice daily for 5 days) oral administration (Savazzi et al. 1986). The elimination half-life of indobufen was higher in elderly patients than in healthy younger volunteers (t1/2 11.6-14.4h vs 6-7h) and plasma drug concentrations were correspondingly higher in the elderly group. This is attributed to the age-related decrease in renal function and a similar dosage reduction to that recommended for patients with renal insufficiency has been recommended in elderly patients (see section 6).

3. Therapeutic Use

The therapeutic value of indobufen’s antiplatelet activity has been examined in patients with occlusive coronary, peripheral and cerebral vascular disease. Platelet activation and aggregation are involved in the pathogenesis of these vascular disorders and their sequelae, including acute myocardial infarction, stroke, peripheral arterial occlusion and venous thromboembolism. The inhibitory effect of indobufen on platelet activation has proven effective in reducing vasoconstriction and vascular occlusion, coronary graft reocclusion and complications in haemodialysis arising from platelet aggregation on the dialysis membrane.

3.1 Treatment of Occlusive Vascular Disease

The efficacy of indobufen in the therapy of intermittent claudication resulting from peripheral vascular disease has been assessed in a number of clinical trials of variable duration.

Indobufen 200mg twice daily significantly improved pain-free walking distance (PFWD) and total walking distance (TWD) in patients with claudication when compared with placebo and baseline values (Belcaro 1990a, b; Signorini et al. 1988; unpublished data on file, Farmitalia Carlo Erba). The results of these studies are summarised in table V.

Signorini et al. (1988) examined the effects of indobufen (200mg twice daily) on PFWD by means of a treadmill exercise test over a 6-month treatment period in a double-blind, placebo-controlled study (fig. 3). Mean PFWD was significantly increased after 6 months in patients receiving indobufen (from 153 to 610m; p < 0.01) and increased, but not significantly, in patients receiving placebo (from 199 to 243m). There was a significant difference (p < 0.01) in mean PFWDs between indobufen- and placebo-treated groups after 6 months. In a larger, more recent study, PFWDs were significantly improved in patients receiving indobufen for 6 months (p < 0.01) compared with those receiving placebo (unpublished data on file, Farmitalia Carlo Erba). Mean PFWDs increased from 138 to 228m following indobufen 200mg twice daily and from 137 to 153m following placebo. Belcaro (1990a, b) also reported an improvement in PFWD following treatment with indobufen (200mg twice daily) in a 10-day crossover study with placebo, and a further improvement in this parameter was observed following combined treatment with indobufen 200mg and defibrotide 400mg twice daily for 20 days (table V).
A single study has compared indobufen (200mg twice daily) with aspirin (500mg twice daily) and no treatment in 204 patients with intermittent claudication over a 1-year period (Belcaro & De Simone 1991; table V). Indobufen was found to significantly (p < 0.05) improve with mean PFWDs and TWDs compared baseline and this improvement was significantly (p < 0.05) greater than that achieved by aspirin. Mean PFWD and TWD values were increased from 746 to 1073m and from 1774 to 1890m, respectively, after 1 year in patients receiving indobufen. It should be noted that the nature of the randomisation controls in this study was uncertain.

In addition to these trials in patients with peripheral vascular disease, indobufen therapy has been associated with a reduction in ischaemic episodes in patients with silent ischaemia in a small (n = 24), nonrandomised study (Pallone et al. 1989). There was a reduction in mean total duration of ischemic episodes and in the mean magnitude of maximum ST segment depression over 3 months in patients receiving indobufen 200mg twice daily compared with patients receiving no treatment; however, the mechanism involved is unclear, and these findings require confirmation in well-controlled studies.

### Table V. Studies comparing the effects of indobufen (INB) 200mg twice daily, indobufen 200mg + defibrotide (DF) 400mg twice daily, aspirin (ASA) 500mg twice daily and placebo (P) in the treatment of patients with intermittent claudication

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>Duration of treatment</th>
<th>Mean PFWD (m)</th>
<th>Mean TWD (m)</th>
<th>VAR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belcaro (1990a)</td>
<td>Nonblind, crossover</td>
<td>18</td>
<td>Baseline</td>
<td>10d</td>
<td>878</td>
<td>1145</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>10d</td>
<td>956</td>
<td>1250</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>INB</td>
<td>20d</td>
<td>1378</td>
<td>1390</td>
<td>16.36</td>
</tr>
<tr>
<td>Belcaro (1990b)</td>
<td>Nonblind, crossover</td>
<td>22</td>
<td>Baseline</td>
<td>10d</td>
<td>850</td>
<td>1170</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>10d</td>
<td>890</td>
<td>1160</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>INB</td>
<td>10d</td>
<td>1193</td>
<td>1304</td>
<td>14.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>INB + DF</td>
<td>20d</td>
<td>1344</td>
<td>1570</td>
<td>32.1</td>
</tr>
<tr>
<td>Belcaro &amp; DeSimone</td>
<td>Nonrandomised,</td>
<td>204</td>
<td>Baseline</td>
<td>1y</td>
<td>746</td>
<td>1774</td>
<td></td>
</tr>
<tr>
<td>(1991)</td>
<td>comparative</td>
<td></td>
<td>P</td>
<td>1y</td>
<td>510</td>
<td>1120</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>INB</td>
<td>1y</td>
<td>1073†</td>
<td>1890†</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ASA</td>
<td>1y</td>
<td>703‡</td>
<td>1520‡</td>
<td></td>
</tr>
<tr>
<td>Signorini et al. (1988)</td>
<td>Randomised,</td>
<td>28</td>
<td>Baseline</td>
<td>3mo</td>
<td>153</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>double-blind</td>
<td></td>
<td>INB</td>
<td>3mo</td>
<td>357</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>INB</td>
<td>6mo</td>
<td>610&quot;</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>3mo</td>
<td>199</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>6mo</td>
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<td>P</td>
<td>6mo</td>
<td>243</td>
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<td>Unpublished data on</td>
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<td>154</td>
<td>Baseline</td>
<td>3mo</td>
<td>136</td>
<td>237</td>
<td></td>
</tr>
<tr>
<td>file, Farmitalia Carlo</td>
<td>randomised,</td>
<td></td>
<td>P</td>
<td>6mo</td>
<td>153</td>
<td>263</td>
<td></td>
</tr>
<tr>
<td>Erba</td>
<td>double-blind</td>
<td></td>
<td>INB</td>
<td>6mo</td>
<td>137</td>
<td>245</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** d = days; m = metres; mo = months; PFWD = pain-free walking distance; TWD = total walking distance; VAR = venoarteriolar reflex (% reduction in skin flow on standing compared to resting); y = year; * = p < 0.05 vs placebo; † = p < 0.05 vs baseline; ‡ = p < 0.05 vs indobufen; ** = p < 0.01 vs placebo.

3.2 Prophylactic Use in Occlusive Vascular Disease

3.2.1 Arterial Bypass Graft Surgery, Carotid Endarterectomy and Coronary Angioplasty

The success of coronary and femoropopliteal ar-
tery bypass grafts is seriously limited by the development of graft occlusion. The frequency of occlusion in saphenous vein grafts was reported as between 12 and 20% during the first year and 2 to 4% annually for the next 4 or 5 years (Campeau et al. 1983; Grondin et al. 1989). Subsequently, this rate doubles, so that after 10 years approximately 50% of grafts become occluded due to the occurrence of graft atherosclerosis.

The pathogenesis of the long term development of graft atherosclerosis is unknown; however, platelet aggregation and TXA2 production may explain early thrombosis of the graft and the resulting intimal thickening may be a precursor to atherosclerosis.

Clinical trials have shown improved graft patency with the use of antiplatelet and anticoagulant drugs such as aspirin, ticlopidine and dipyridamole during the first postoperative year (Fuster & Cheesbro 1985; Limet et al. 1987). Recent studies have found indobufen to be at least as effective in reducing the frequency of graft occlusion as other platelet inhibitors.

The effects of indobufen on coronary artery bypass graft (CABG) patency over 1 year were recently examined in a multicentre, randomised, double-blind study of 569 patients (SINBA Group 1991). Daily administration of indobufen 400mg starting 6 hours after surgery was at least as effective as aspirin 900mg plus dipyridamole 225mg daily in preventing graft occlusion (fig. 4). Early occlusion (within 1 month) of 1 or more grafts occurred in 22.7% (n = 34) of patients receiving indobufen compared with 23.4% (n = 34) in the aspirin + dipyridamole group, and after 1 year 34.2% (n = 69) of indobufen-treated patients had graft occlusion compared with 34.4% (n = 62) of patients receiving aspirin + dipyridamole (95% confidence limit = 0.65 to 1.56). This initial study has indicated that indobufen may improve CABG patency; further investigation in this indication has recently been carried out in a randomised, double-blind study involving 552 patients (unpublished data on file, Farmitalia Carlo Erba). Indobufen 400mg daily improved graft patency to a similar extent as aspirin 900mg + dipyridamole 225mg daily 1 year after CABG surgery with all grafts patent in 56% of indobufen-treated patients and in 59% of aspirin-dipyridamole recipients.

Graft patency following revascularisation of the lower limbs using prosthetic or reversed saphenous vein grafts is significantly affected by thrombotic occlusion. Inhibition of platelet function by a combination of aspirin and dipyridamole improves patency rates of femoropopliteal bypass grafts when compared with placebo (Donaldson et al. 1985; Green et al. 1982). The efficacy of indobufen 200mg twice daily has been compared with that of aspirin 300mg plus dipyridamole 75mg thrice daily in the prevention of occlusion in a polytetrafluoroethylene (PTFE) graft following administration for 1 and 12 months (Curti 1989). Graft patency was comparable between treatment groups after 1 month, with mean patency rates of 94.6% in the indobufen-treated patients (n = 56) and 98.3% in patients who received aspirin plus dipyridamole (n = 57). After 1 year of treatment, patency rates were 60.0% and 53.2%, respectively.

Antiplatelet drugs have proven useful in decreasing the incidence of carotid artery thrombosis following reconstructive surgery for atherosclerotic carotid occlusive disease (Edwards et al. 1985). Internal carotid artery occlusion has been reported in approximately 5% of patients during the immediate period following surgery and late restenosis occurs in 1 to 30% of cases (Ortega et al. 1981;
Salenius et al. 1989; Stoney & String 1976). In a double-blind, placebo-controlled trial, Pratesi et al. (1991) administered indobufen 400mg daily or placebo to 20 patients undergoing carotid endarterectomy, starting 2 days before surgery and continuing for 6 months thereafter. Platelet accumulation and aggregation in carotid endarterectomy was assessed by means of scintigraphy using \(^{111}\)In-labelled platelets. Postoperative scintigraphy failed to detect any significant platelet accumulation or aggregation in patients treated with indobufen whereas this was evident in 4 of 10 patients in the placebo group. Angiographic analysis performed intraoperatively at the end of surgery and venous angiography performed at the end of the study revealed 2 patients with stenotic relapse and 1 patient with carotid occlusion in the placebo group but there were no lesions of any significance in the indobufen-treated group. While a larger trial is necessary to confirm these findings, they suggest that indobufen therapy, starting before surgery and continuing for at least 6 months postsurgery, may help prevent thrombosis following carotid endarterectomy.

The effect of indobufen 400mg twice daily or aspirin 325mg 3 times daily on the incidence of recurrent stenosis has been investigated in 323 patients following percutaneous transluminal coronary angioplasty (Dalla Volta 1989). Both drugs were similarly effective in preventing recurrent stenosis over a 6 month period, with 31% of patients receiving indobufen and 38% of patients receiving aspirin showing restenosis.

3.2.2 Transient Ischaemic Attack and Stroke
Thrombotic and embolic complications of atheroma are considered to be the main cause of severe cardiovascular and cerebrovascular events in patients following a transient ischaemic attack (TIA) or mild stroke.

The efficacy of indobufen in the secondary prevention of TIA and stroke has been assessed over a 12-month treatment period in a noncomparative study of 270 patients with a history of one or more episodes of TIA within the 3 months prior to the commencement of the study (Rogan et al. 1990). The average incidence and number of recurrent TIsAs declined significantly (p < 0.001) after 1 month of therapy with indobufen (100mg twice daily) and remained decreased for the remainder of the study. Treatment was not effective in approximately 5% of the patients.

Fornaro et al. (1990) have reported a significant (p < 0.05) decrease in the incidence of fatal and nonfatal thromboembolic events compared with placebo following 26 months of indobufen therapy (100mg twice daily) in 196 patients with heart disease (90 with atrial fibrillation and 106 in sinus rhythm). The incidence of events in the indobufen-treated group was 5% compared with 15% in the placebo group. In a nonrandomised retrospective study (Belcaro et al. 1990d), indobufen therapy was associated with a lower incidence of 'new cardiac events' (2.34%) in a group of 638 patients with cerebrovascular disease, compared with a 6% incidence in a similar control group of 50 patients who received no treatment. The incidence of events in the indobufen group was also significantly lower than that in patients receiving either aspirin 250mg twice daily (2.8%; n = 265) or dipyridamole 75mg twice daily (2.9%; n = 174) [Belcaro et al. 1990d].

In another study, Rodriguez et al. (1989) failed to find any significant difference in the incidence of new cerebrovascular events between patients receiving either indobufen 200mg twice daily (n = 51) or aspirin 500mg twice daily (n = 52) for a mean of 21 weeks.

These studies suggest that the platelet inhibitory activity of indobufen may improve the prognosis of patients after a transient ischaemic attack or mild stroke.

3.2.3 Deep Vein Thrombosis
The efficacy of indobufen in the prevention of recurrent deep vein thrombosis (DVT) has been investigated over a 3-year period in a randomised trial of 123 patients following an episode of DVT (Belcaro et al. 1992). The incidence of thrombosis in the group of patients receiving indobufen 200mg twice daily was significantly lower (p < 0.02) than in the group receiving no treatment (5 and 46%, respectively).
The development of DVT is common in patients following acute myocardial infarction, occurring with an incidence of approximately 30%. Because of the role of platelets in the pathogenesis of thrombosis, the use of indobufen in the prophylaxis of DVT has been investigated in patients with acute myocardial infarction, in comparison with the oral anticoagulant acenocoumarol (Peters et al. 1982). In this double-blind prospective study, 150 patients were administered indobufen 200mg twice daily or acenocoumarol for 10 days, starting within 24 hours of the acute event. Screening for the development of DVT was by 

\[ \text{[I}^{125}\text{]}\text{-fibrinogen leg scanning. No significant difference was found between the incidence of DVT in indobufen- (11%) and acenocoumarol-treated patients (9%).}

These findings suggest that indobufen may be effective in the prophylaxis of DVT and that further larger studies of the drug in this indication are warranted.

### 3.2.4 Haemodialysis

Platelet adhesion and activation occurs on the dialysis membrane during haemodialysis in patients with chronic renal failure. The resulting microthrombus formation leads to a reduction in dialyser efficiency and may contribute to increased blood loss during dialysis. The antiplatelet drugs aspirin and dipyridamole have both shown favourable results in preventing thrombus formation and platelet deposition on the dialysis membrane (Salter et al. 1985).

Plasma levels of the platelet markers BTG and PF4 are elevated in patients with chronic renal failure and are further increased during haemodialysis (Green et al. 1980; Pogliani et al. 1979). The effect of indobufen on platelet activation during haemodialysis has been determined by monitoring plasma levels of BTG and PF4, and by using scanning electron microscopy to monitor platelet deposition on the membrane (Buccianti et al. 1982; Pogliani et al. 1982; Salter et al. 1985). Intravenous administration of indobufen (100mg) 30 minutes before starting haemodialysis reduced levels of BTG and PF4 compared with placebo (Pogliani et al. 1982). This reduction was significant after 30 minutes, at which point the BTG levels were 145 µg/L following indobufen and 180 µg/L following placebo A; PF4 levels after indobufen and placebo were 88 and 134 µg/L, respectively.

In a double-blind crossover study, 18 haemodialysis patients received placebo, indobufen 100 or 200mg for 7 days with a washout period of 7 days between treatments (Salter et al. 1985). There was a significant reduction in mean platelet count and a significant increase in mean BTG levels during dialysis in the placebo group, whereas both doses of indobufen were equally effective in inhibiting platelet function. Scanning electron microscopy of membranes following treatment found significantly more platelet deposition after placebo administration than after indobufen treatment (p < 0.05), with an average of 51.5% of membrane occluded following placebo and 30% following indobufen. There was no significant difference between the effects of the 2 doses of indobufen on platelet deposition.

Indobufen therapy may therefore prove useful during haemodialysis in preventing platelet aggregation on the dialysis membrane, subsequently improving the efficiency of the haemodialyser.

### 3.2.5 Migraine

Abnormal platelet activity has been implicated in the pathogenesis of migraine, and antiplatelet agents may be useful in its prophylaxis (Hannington 1981; Steiner et al. 1985). In one initial double-blind, placebo-controlled study of 62 patients with classic or common migraine, indobufen therapy (200mg twice daily) was associated with a significant reduction in both the frequency and duration of migraine attacks, suggesting a potential benefit of the drug (Carrieri et al. 1988).

### 4. Tolerability

Indobufen 200mg twice daily has been very well tolerated in the majority of patients during short and long term clinical trials. In a postmarketing surveillance study conducted by the manufacturer (Lavezzari et al. 1989), the adverse effects of indobufen were evaluated in more than 5560 patients.
with atherosclerotic disease over a 3-month treatment period. Adverse effects were reported in 220 patients (3.9%), necessitating treatment withdrawal in 103 patients (1.9%). A broadly similar incidence of adverse effects has been reported in smaller studies of longer duration (Belcaro et al. 1990d; Rogan et al. 1990; SINBA Group, 1991). In these studies indobufen (200mg twice daily) was administered over a 12-month period and incidences of adverse effects ranged between 3.2 and 9%. However, one noncomparative multicentre study reported a higher incidence of adverse effects (23%) over a 2-year treatment period in 151 patients with occlusive vascular disease (Italian Multicentre Study Group 1985).

The most commonly reported adverse effects associated with indobufen were gastrointestinal, which accounted for approximately 80% of the total drug-related effects (Italian Multicentre Study Group 1985; fig. 5). These included dyspepsia (32% of total reported effects), abdominal pain (21%), constipation (9%), nausea and vomiting (10%). Haemostasis and coagulation disorders associated with indobufen therapy have been reported in a small number of patients (0.4%). Similarly low incidences of skin and CNS disorders have been reported (Lavezzari et al. 1989). Haemostatic adverse effects accounted for 8%, CNS effects 3% and skin disorders 7% of total adverse effects.

In comparative studies in patients with coronary and cerebral vascular disease a lower incidence of adverse effects in patients receiving indobufen 200mg twice daily has been apparent compared with the incidence in patients receiving aspirin 350mg plus dipyridamole 75mg 3 times daily (9 and 18%, respectively; SINBA Group 1991). Adverse effects in patients receiving indobufen were generally less severe and subsequently the percentage of patients discontinuing treatment was lower than in the other treatment groups.

5. Drug Interactions

There are few investigations of drug interactions involving indobufen. Pretreatment with indobufen 200mg twice daily has been reported to significantly (p < 0.05) increase plasma glipizide concentrations after single dose administration of oral glipizide 5mg to 6 healthy volunteers (Elvander-Ståhl et al. 1984), an effect possibly attributable to an inhibitory effect of indobufen on glipizide metabolism. This finding implies that dosage adjustment of glipizide may be necessary when co-administered with indobufen.

Indobufen did not influence the pharmacokinetic properties of the β-adrenoreceptor antagonists propanolol 80mg or atenolol 100mg when each drug was administered to separate groups of 6 volunteers (Elvander-Ståhl et al. 1984).

6. Dosage and Administration

The recommended daily dosage of indobufen is 100 to 200mg orally twice daily after meals.

Dosage reduction to 100mg twice daily in patients with mild to moderate renal impairment (creatinine clearance 30 to 80 ml/min) and to 100mg once daily in patients with moderate to severe renal impairment (creatinine clearance < 30 ml/min) is recommended. Similar dose reductions are recommended for the elderly based on creatinine clearance rates.

7. Place of Indobufen in Therapy

Indobufen is a platelet aggregation inhibitor which may be useful in the management of thrombosis. Studies have shown indobufen to be an ef-
fective antiplatelet agent which, unlike aspirin, causes reversible inhibition of platelet cyclo-oxygenase, while having no apparent clinically significant effects on any haemodynamic parameters.

The majority of clinical studies to date have examined the therapeutic efficacy of indobufen in patients with peripheral vascular disease and its prophylactic use in patients following revascularisation surgery.

Placebo-controlled randomised studies have found a significant and sustained increase in pain-free and total walking distances following indobufen therapy in patients with intermittent claudication, and initial findings in a nonrandomised, short term study suggest that indobufen has a more pronounced ameliorative action than aspirin in this setting; however, this observation remains to be confirmed in well-controlled studies. In addition, the relative efficacies of indobufen and ticlopidine in peripheral artery disease remain to be established.

The clinical significance of the apparent beneficial effect of indobufen on microcirculatory parameters found in studies in patients with peripheral vascular disease or diabetes has yet to be determined.

Indobufen 200mg twice daily appears to be significantly more effective than placebo in preventing vascular reocclusion following carotid endarterectomy and femoropopliteal bypass surgery, and at least as effective as aspirin 975mg daily in combination with dipyridamole 225mg daily in improving coronary artery bypass graft patency.

In addition to its use in the treatment of intermittent claudication and prevention of arterial graft occlusion, the efficacy of indobufen for secondary prevention of vascular events following myocardial infarction or transient ischaemic attack has been investigated in a small number of controlled studies. While these studies have indicated a potential benefit of indobufen in reducing the incidence of secondary attacks over a 3-year period, further long term studies are required to confirm the prophylactic efficacy of indobufen and its influence on patient prognosis.

An initial study has found indobufen therapy to be effective in decreasing the frequency and duration of migraine attacks, suggesting that the drug may have a beneficial effect on the prophylaxis of migraine, and further investigation is warranted. Indobufen may also be effective in the prevention of thrombus formation on haemodialysis membranes, a major problem during haemodialysis which results in decreased efficiency and increased blood loss.

Aspirin is currently the most widely used antiplatelet drug; however, adverse effects are frequently associated with its use. These effects are mainly gastrointestinal and occur in approximately 10 to 15% of patients receiving aspirin at dosages in excess of 300 mg/day. Direct comparisons of the tolerabilities of indobufen and aspirin have found a lower incidence of adverse effects and drug discontinuation in patients receiving indobufen. It should be noted that in these studies aspirin was administered at high doses (975mg daily) and as aspirin appears to be equally effective at lower doses in the prevention and treatment of occlusive vascular disease, a comparison of the incidences of gastrointestinal and haemorrhagic effects following low dose aspirin (150 to 300mg daily) and indobufen is required before the relative tolerabilities of the 2 compounds can be properly assessed.

Although indobufen has demonstrated comparable efficacy to aspirin in improving graft patency rates in patients following revascularisation surgery, well-controlled, prospective studies are required to compare the efficacy of the 2 drugs in patients with intermittent claudication.

Thus, initial studies have shown an improvement in arterial graft patency associated with indobufen and have demonstrated a beneficial effect of the drug in patients with intermittent claudication. Although these findings remain to be confirmed in larger, well-controlled studies of longer duration, it would seem that indobufen offers potential benefits in the therapy and prophylaxis of occlusive vascular disease. Further, because of its low incidence of gastrointestinal and haemorrhagic effects, indobufen may represent a suitable alternative to high dose aspirin for long term use in this indication.
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