Pharmacokinetics of Low-Dose Oral Modified Release, Soluble and Intravenous Aspirin in Man, and Effects on Platelet Function

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Summary. The pharmacokinetics of low-dose aspirin and the resulting salicylic acid were studied in 6 healthy volunteers. Each received a single 50-mg dose of (1) oral modified release capsules, (2) oral solution and (3) intravenous solution. The volunteers also received 50 mg modified release capsules daily for 6 days to determine the effect on collagen, ADP and arachidonate induced platelet aggregation and thromboxane production, and to compare the pharmacokinetics after repeated dosing with the parameters obtained after the single dose.

The formulation and route of administration profoundly influenced several pharmacokinetic parameters for aspirin: the maximum concentration (Cmax, ng·ml⁻¹) was 221 and 191 after modified release for single and chronic dosing respectively, 1323 after the oral solution and 6000 after intravenous injection; the time to achieve this maximum concentration (tmax, h) was 3.42 and 3.02 after modified release for single and chronic dosing respectively, and 0.29 after the oral solution; the area under the plasma drug concentration versus time curve (AUC, μg·h·ml⁻¹) was 0.38 and 0.27 after modified release single and chronic dosing respectively, 0.68 after the oral solution and 1.57 after intravenous injection.

The elimination of aspirin after the two solutions was at least biphasic. The terminal phase rate constant ranged from 1.52 h⁻¹ after intravenous injection to 1.88 h⁻¹ after the oral modified release form. The absorption of the oral forms of aspirin was complete as reflected by the total recovery of the doses as salicylic acid in urine. The pharmacokinetic parameters for salicylic acid showed similar tmax and Cmax for the oral solution and intravenous injection but, as for aspirin, Cmax was least and tmax greatest when the modified release form was used.

After 7 days of modified release aspirin platelet aggregation and thromboxane formation in response to collagen and arachidonate were markedly inhibited. There was no inhibition of ADP-induced aggregation, but thromboxane production in response to ADP was abolished.

Key words: aspirin, salicylic acid; low-dose aspirin pharmacokinetics, platelet function

Aspirin is being increasingly used for prophylaxis against arterial thrombo-embolic disorders, such as unstable angina, cerebral transient ischaemic attacks, and rethrombosis following coronary artery bypass grafts (Gallus 1985; Antiplatelet Trialists' Collaboration 1988). Dosage regimens in the various trials which have demonstrated benefit from aspirin have been variable. Daily aspirin dosages have ranged from 1.3 g in patients with cerebrovascular disease (Fields et al. 1977) to 324 mg in patients with unstable angina (Lewis et al. 1983). Little attention has been paid to the formulation of aspirin, and in most trials, where stated, this has been ordinary or compressed aspirin. There has been increasing interest recently in employing aspirin doses even smaller than 100 mg daily, based on observations which have suggested that inhibition of thromboxane synthesis might be achieved by smaller doses than those required for inhibition of prostacyclin synthesis (Burch et al. 1978; Hanley et al. 1981; Preston et al. 1981). Furthermore, there is interest in the possibility that slow release, enteric coated (modified release) formulations may deliver aspirin to the portal circulation at a slow enough rate to allow substantial deacetylation of aspirin during its first pass through the liver (Ali et al. 1980; Siebert et al. 1983). This may achieve the potentially desirable effect of inhibition by aspirin of thromboxane
generation in platelets during their passage through the portal circulation whilst sparing systemic vascular endothelial prostacyclin production (Siebert et al. 1983; Pedersen and FitzGerald, 1984). We have recently shown that modified release aspirin resulted in maximum inhibition of platelet function when given in doses of 60–80 mg daily for 2 weeks (Herd et al. 1987).

The pharmacokinetics of aspirin which are achieved by oral modified release aspirin doses of less than 100 mg daily have been difficult to determine because of inadequate assay sensitivity (Rumble et al. 1981). Assays have been reported with adequate sensitivity to determine the disposition of aspirin given intravenously or as oral solution (Pedersen and FitzGerald 1985), or as a highly soluble rapid release oral preparation (Brandon et al. 1985). A more sensitive assay, recently developed in our laboratory, is capable of measuring aspirin to 2 ng/ml (Siebert and Bochner 1987). We were interested, therefore, to determine the pharmacokinetics of aspirin after ingestion of single doses of modified release 50-mg form. It was considered important to compare the behaviour of this formulation with the same dose given as intravenous and oral solutions. In addition, the pharmacokinetics and effect on platelet function were studied after chronic dosing for 1 week with 50 mg modified release aspirin.

**Methods**

**Subjects**

Six healthy subjects (5 males, 1 female) aged 21–46 years, weighing 47.5–66 kg were studied. The subjects abstained from any medication known to alter platelet function throughout the study period. Three of the 6 subjects were cigarette smokers. The subjects had a light breakfast about 1 h prior to aspirin ingestion, and lunch about 4 h later. All were normal as assessed by medical examination, complete blood examination, and multiple blood biochemistry. These studies were approved by the Ethics Committees of the Royal Adelaide Hospital and the University of Adelaide.

**Protocol**

Each subject received in balanced random order a single dose of 50-mg aspirin as an intravenous infusion over 1 min, as an oral solution, and as modified release pellets in gelatin capsules (Astrix, F.H. Faulding & Co. Limited, Adelaide, South Australia). In the chronic dosing study, each subject took 50 mg of the modified release form daily for 6 days at 8.00 a.m. On the seventh day, blood was collected for measurement of platelet function and predose aspirin and salicylic acid concentrations prior to the dose (9.00–10.00 a.m.) and pharmacokinetic study. There was an interval of at least 1 week between each single dose study, and at least 1 month between the last single dose and the chronic dosing study.

Venous blood was sampled via an indwelling 18-gauge teflon cannula (Jelco, Critikon Inc., Tampa, Fla). Patency of the cannulae was maintained by insertion of a plastic stylet (Jelco, Critikon Inc., Tampa, Fla). Five ml blood samples were collected prior to aspirin administration and at specified times for 7 h after modified release aspirin, and 6 h after the 2 solutions. The nominated times were 5, 10, 20, 30, 45, 60 min, 1.25, 1.5, 2, 3, 4, 5 h after the administration of the oral solution and after completion of the 1-min infusion and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6 and 7 h after the modified release form. Urine was collected for 24 h after each single dose.

**Aspirin Formulation**

The intravenous form was prepared as a sterile solution by the staff of the Pharmacy Department, Royal Adelaide Hospital. The pH of the solution was adjusted to 6.5 with sodium bicarbonate, 1 g/100 ml. This formulation was infused within 1 h of preparation, although it was shown to be stable for at least 8 h (chemical hydrolysis of less than 5%). The oral solution was prepared by dissolving 50 mg pharmaceutical grade aspirin (Monsanto, Australia) in 100 ml 0.1 M sodium bicarbonate on the day of use. The modified release form was given as Astrix 50 mg.

**Assays**

(1) **Aspirin.** Five millilitres of blood was collected into chilled 10 ml heparinized tubes containing 100 µl of a 40 mM physostigmine hemisulphate solution. The plasma was separated immediately and stored frozen until assay within 2 weeks (Cham et al. 1980). Assay of aspirin was carried out as reported by Siebert and Bochner (1987).

(2) **Salicylic acid** was measured in plasma and urine by the method of Siebert and Bochner (1987) with slight modifications in the extraction proce-