Bioinequivalence of Four 100mg Oral Aspirin Formulations in Healthy Volunteers

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Summary
The single dose pharmacokinetics of 4 commercially available 100mg oral aspirin formulations were studied in 6 healthy men and 6 healthy women. Two of the formulations were rapid release (‘Cardiprin’ 100, ‘Platelin’) and the other 2 were enteric coated formulations (‘Astrix’ 100, ‘Cartia’). There were marked differences in the plasma concentration-time profiles between the rapid release and the enteric coated formulations. There were no significant differences (p > 0.05) in the mean time to achieve maximum aspirin concentrations between ‘Cardiprin’ 100 (0.35h) and ‘Platelin’ (0.35h), but this was significantly prolonged (p < 0.001) for ‘Astrix’ 100 (3.73h) and even more prolonged for ‘Cartia’ (6.84h). Similar between-formulation differences were seen in the areas under the plasma concentration-time curves, for which the rank order was ‘Cardiprin’ 100 (1.60 mg/L • h) = ‘Platelin’ (1.54 mg/L • h) > ‘Astrix’ 100 (0.73 mg/L • h) > ‘Cartia’ (0.56 mg/L • h). For ‘Cardiprin’ 100, ‘Platelin’ and ‘Astrix’ 100 plasma aspirin concentrations were below 5 µg/L by 7h after ingestion, whereas for ‘Cartia’ aspirin was detectable for up to 16h, giving the appearance of sustained release. The enteric coated formulations produced the greatest variability in the plasma aspirin concentration vs time profiles. The urinary recovery of salicylate was greater than 80% of the administered dose for all 4 formulations. The clinical significance of the marked pharmacokinetic differences observed with these 4 low-dose aspirin formulations is not known.

Low aspirin dosages (<300 mg/day) are being used increasingly to manage and prevent various vascular occlusive disorders. Recently, enteric coated aspirin 162.5mg daily has been shown to reduce the mortality and rate of reinfarction after myocardial infarction (ISIS Collaborative Group 1988). The advantages of using even lower dosages and slow release or enteric coated formulations are still controversial, but are based on observations which have suggested that inhibition of thromboxane synthesis might be achieved by smaller doses than those required to inhibit prostacyclin synthesis (Burch et al. 1978; Hanley et al. 1981; Knapp et al. 1988; Pedersen & FitzGerald 1984; Preston et al. 1981; Vial et al. 1990). The debate is further complicated by the fact that the inhibitory effects of aspirin on vascular cyclooxygenase are reversible, while the effects on platelet cyclooxygenase are irreversible, lasting the lifespan of the platelet (Weksler et al. 1985). A knowledge of the concentration-time profile of aspirin could therefore be important, since modification of dosage regimens and formulations may exploit the potential advantages of the differential inhibitory effects of aspirin on platelets and vessel walls.

There are now several low dose (< 100mg) as-
pirin formulations available in many countries, including Australia, where 4 such preparations are used specifically for the prevention of thromboembolic disorders. Until recently, it was not possible to measure plasma aspirin concentrations after low doses because of inadequate assay sensitivity. We report here on the absorption and disposition of 4 aspirin 100mg formulations, 2 of which are rapid-release, and 2 are enteric coated formulations.

**Methods**

**Subjects and Protocol**

12 healthy drug-free adult volunteers gave written informed consent to participate in this study, which was approved by the Committee on the Ethics of Human Experimentation of the University of Adelaide and the Royal Adelaide Hospital Human Ethics Committee. There were 6 men and 6 women; their ages ranged from 19 to 38 years and they weighed between 51 and 71 kg. Prior to and on completion of the study each volunteer underwent a full medical history and physical examination, and blood was drawn for biochemical and haematological analyses.

The study used a 4-way randomised single-dose crossover design. There was an interval of between 4 and 14 days between each dose. Volunteers were divided into 3 groups of 4 volunteers each (Wagner 1975). The 100mg aspirin formulations were: ‘Cardiprin’ 100 (Reckitt and Colman Pharmaceuticals, West Ryde, Australia), a rapid release tablet; ‘Platelin’ (Nicholas Australia, Chadstone, Australia), a rapid release tablet; ‘Astrix’ 100 (F.H. Faulding and Co. Limited, Adelaide, Australia), enteric coated granules in a capsule formulation; and ‘Cartia’ [Smith, Kline & French Laboratories (Australia) Ltd, French’s Forest, Australia], an enteric coated tablet.

Each volunteer reported to the Clinical Trials Laboratory after an overnight fast of 10 h. An intravenous teflon catheter (Jelco®, Critikon Inc., Tampa, Fla., USA) was inserted into a forearm vein and kept patent with a teflon stylet (Jelco). Each formulation was ingested with 100 ml of tap water. A 5 ml venous blood sample was taken prior to drug administration and then at the following designated times: for ‘Platelin’ and ‘Cardiprin’ 100, 5, 10, 20, 30 and 45 min and 1, 1.25, 1.5, 2, 3, 4 and 5 h after administration; for ‘Astrix’ 100, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7 and 8 h after administration; for ‘Cartia’, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 16 h. These sampling protocols were determined after a pilot study. Due to the nature of the concentration-time profile resulting from ‘Cartia’, this product was administered at about 0600 h (after an overnight fast) and no baseline (0 h) blood sample was obtained prior to drug ingestion. The volunteers were confined to the laboratory and remained ambulant throughout the sampling period. A cup of coffee or tea was provided after the 2 h blood sample, lunch was provided after the 4 h sample and an evening meal after about 8 h. An identical meal was provided to each volunteer on each occasion. Each volunteer collected all urine for 48 h after drug ingestion. After collection of the blood samples into heparinised blood collection tubes (containing 0.05 ml of an 80 mmol/L physostigmine solution to prevent hydrolysis of aspirin to salicylate), the blood was centrifuged at 3500 rpm for 10 min and the plasma was removed and frozen (−20 °C) until analysed (within 14 days of collection). Under these conditions there is less than 10% hydrolysis of aspirin (Cham et al. 1980).

**Drug Assays**

Plasma aspirin concentrations were measured by the high performance liquid chromatography (HPLC) method of Siebert and Bochner (1987). The intraday reproducibility as assessed by the coefficient of variation of the assay was 8.6% at 19 μg/L (n = 6) and 6.7% at 1900 μg/L (n = 6). Accuracy at 19 μg/L was 80% and at 1900 μg/L was 91%. The limit of quantification was 5 μg/L. Urine salicylate concentrations were measured according to the method of Bochner et al. (1988) after the urine samples had been subjected to heat and acid hydrolysis (Levy et al. 1972).