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DIFLUNISAL: A REVIEW OF PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES, DRUG INTERACTIONS, AND SPECIAL TOLERABILITY STUDIES IN HUMANS

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1 In the fasting state, peak plasma levels of diflunisal were achieved within 2 hours. The drug was not metabolized and almost totally excreted in the urine as unchanged or conjugated drug. The terminal plasma half-life was approximately 8 hours. These results support a twice daily dose regimen.

2 During multiple dose administration the time required to achieve steady-state plasma levels varied with the dose. A dose regimen of 125 mg twice daily required 2–3 d, whereas a regimen of 500 mg twice daily required 7–9 d to reach a steady-state plasma level.

3 Clinically effective doses of diflunisal decreased the urinary excretion of the major prostaglandin E metabolite, 7α-hydroxy-5,11-diketotetranorprostane-1,16-dioic acid, and exhibited significant uricosuric activity. These same doses did not seem to cause tinnitus, nor did they significantly alter gastrointestinal blood loss, affect blood glucose, bleeding time, or platelet function.

4 Clinically significant drug interactions may be anticipated during concomitant administration with at least one oral anticoagulant (acenocoumarol), but probably not anticipated during the coadministration of oral antidiabetic agents, thiazide diuretics, and non-steroidal anti-inflammatory/analgesic agents.

5 Clinical and laboratory data accumulated during these studies indicated that diflunisal was well tolerated.

Introduction

This review of the clinical pharmacology of diflunisal (2',4'-difluoro-4-hydroxy-3-biphenylcaboxylic acid) summarizes data generated in 23 separate studies carried out in Belgium, Italy, The Netherlands, Switzerland, and the United States. It is anticipated that the unpublished studies reported here will subsequently be published in greater detail.

Pharmacokinetics and metabolism

Single dose kinetics

In the fasting state diflunisal was well absorbed after oral administration with peak plasma levels being reached within 2–3 h (Steelman *et al.*, 1975). The presence of food in the stomach slightly delayed, but did not decrease the absorption of diflunisal (Figure 1).

The initial plasma half-life following single oral doses of diflunisal 125, 250 or 500 mg seemed to be dose dependent, ranging from approximately 7.5 h for the 125-mg dose to 11 h for the 500-mg dose. The terminal slope determined after plasma drug levels reached approximately 15 μg/ml indicated a half-life of 7.5–8 h in subjects with normal renal function.

In a study using radiolabelled diflunisal, 95% of oral doses were excreted in the urine, with 85–90% of the urinary diflunisal appearing as one of two highly soluble glucuronide conjugates. Diflunisal was not metabolized either by cleavage of the two aromatic rings or by a loss of fluoride atoms (Tocco *et al.*, 1975). About 5% of the dose was recovered in the faeces. Although diflunisal has been shown to appear in bile from rats treated with this drug (Breault, unpublished observations), comparable data for man are not available to determine whether the diflunisal in the faeces is unabsorbed drug or represents biliary excretion.

Tjandramaga (unpublished observations) has studied the plasma pharmacokinetics of diflunisal in various stages of renal failure and has demonstrated that as the creatinine clearance was reduced, the plasma half-life of diflunisal increased. Figure 2 shows that marked prolongation of the plasma half-life did not occur until renal function was severely compromised.

Data generated following single doses indicated that diflunisal was tightly bound (approximately 98%) to

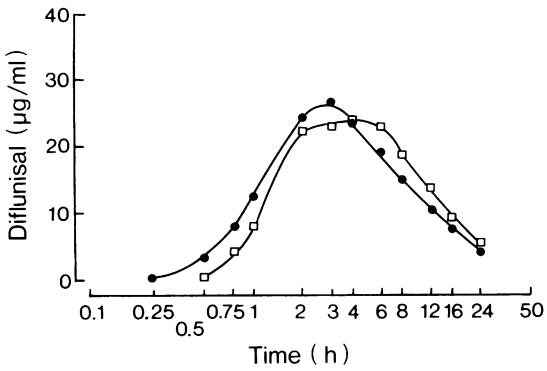

Figure 1 Mean concentrations of diflunisal in plasma obtained from 18 normal male subjects after a single oral dose of diflunisal 250 mg in fasting (●) and non-fasting states (□).

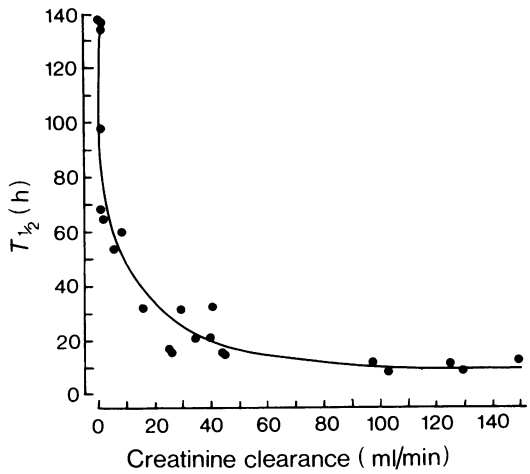

Figure 2 Diflunisal plasma half-life ($T_{\frac{1}{2}}$), after a single oral 500 mg dose, in five normal subjects and 17 patients with varying degrees of renal impairment.

plasma protein. Haemodialysis is not an efficient means of removal of diflunisal (Tjandramaga, unpublished observations). When diflunisal was administered to lactating women (Steelman *et al.*, 1975), the drug appeared in their milk at concentrations of 2–7% of that found in their plasma.

Multiple dose kinetics

The time required to reach a steady-state level of diflunisal in plasma increased as the dose of drug was increased. A dose regimen of 125 mg every 12 h produced a plasma steady-state trough level (the trough plasma level is the plasma level immediately before the next dose) of 12–13 μg/ml after 3 days. A dose regimen of 250 mg every 12 h required 4–5 d to reach a plasma steady-state trough level of 38–40 μg/ml (Steelman *et al.*, 1975). Data obtained for a dose regimen of 375 mg every 12 h for 4–5 d was consistent with the above, in that a steady-state level was not achieved. Projection of these data indicated that 7–9 d would be required before a plasma steady-state level of 65–75 μg/ml was reached (Figure 3). In a separate study, the administration of diflunisal 500 mg twice daily to five subjects produced mean trough levels of approximately 75 μg/ml after 4 d and 85 μg/ml after 7 d (Smit Sibinga, unpublished observations). The steady-state level produced by 500 mg twice daily was projected to be 80–90 μg/ml.

The initial mean plasma half-life for diflunisal following multiple dose regimens of 250 mg twice daily for 7 d and 375 mg twice daily for 4–5 d, was 11–12 h and, consistent with the single dose data, the terminal phase half-life was approximately 7 hours.

As measured by trough plasma levels, the administration of diflunisal 250 mg every 12 h for 21 days did not result in any additional drug accumulation beyond that observed at 5 days (Perrier, unpublished observations).

Pharmacodynamics

General

To compare the various pharmacodynamic characteristics of diflunisal with those of currently available non-steroidal anti-inflammatory/analgesic agents, studies were carried out to determine the effect(s) of therapeutic doses of diflunisal on the urinary excretion of a prostaglandin (PG) metabolite (7α-hydroxy-5, 11-diketotetranorprostane-1, 16-dioic acid), various parameters of uric acid metabolism, platelet function, blood coagulation, and blood glucose.

Urinary prostaglandin excretion

Within 48 h of initiation of a dose regimen of diflunisal 375 mg every 12 h, the urinary excretion of 7α-hydroxy-5,11-diketotetranorprostane-1,16-dioic acid, the major human urinary metabolite of PGE_1 and PGE_2, was decreased by approximately 70% (Steelman *et al.*, 1976). This effect persisted for the 5-day drug treatment period. The magnitude of this decrease was similar to that recorded after administration of either acetylsalicylic acid (ASA) 3 g/d or indomethacin 200 mg/d (Hamberg, 1972).

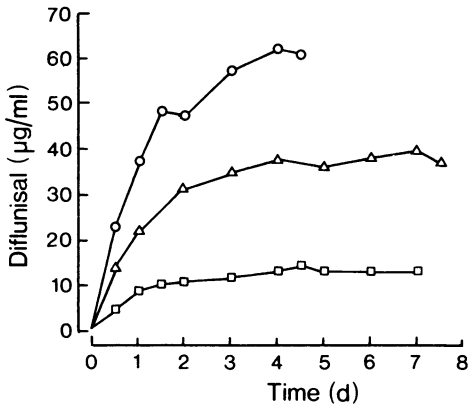

Figure 3 Mean trough concentrations of diflunisal in plasma obtained from normal male subjects on multiple dose regimens of diflunisal. O, 375 mg twice daily ($n=5$); △, 250 mg twice daily ($n=18$); □, 125 mg ($n=18$).

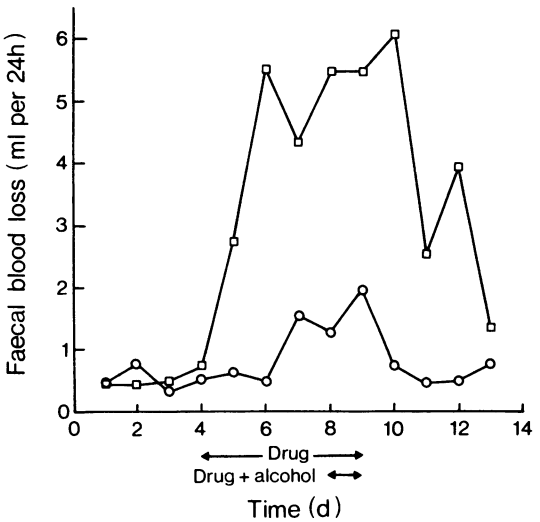

Figure 4 Mean gastrointestinal blood loss experienced by 12 normal male subjects after administration of equianalgesic doses of ASA 2.4 g/day (□) and diflunisal 500 mg/day (O).

Uric acid excretion

Administration of diflunisal 250 or 375 mg every 12 h resulted in an increased renal clearance of uric acid. Serum uric acid levels were significantly decreased on both dose regimens (Dresse *et al.*, 1975; Tempero *et al.*, 1976). ASA, at doses of 2 g/d or less, has been reported to cause uric acid retention, whereas doses of approximately 5 g/d or more exhibit uricosuric activity (Yü & Gutman, 1959).

Platelet function

Many non-steroidal anti-inflammatory/analgesic agents exert effects on platelet function and blood coagulation through their inhibitory actions on the PG synthetase (cyclo-oxygenase) enzyme system (Hamberg *et al.*, 1974), particularly the formation of thromboxane A_2 (Hamberg *et al.*, 1975). ASA decreases the ability of platelets to respond to aggregation stimuli and this effect persists for the life of the platelet. Indomethacin, in contrast, seems to exert a reversible inhibition of platelet aggregation; the effect of indomethacin disappeared within 12–24 h after termination of indomethacin treatment (Smit-Sibinga *et al.*, 1975). In contrast to the above, diflunisal, at single doses as high as 500 mg and chronic dose regimens up to and including 500 mg twice daily, caused no alteration in ADP-induced platelet aggregation, platelet disaggregation or prothrombin and bleeding times (Smit Sibinga *et al.*, 1976; Steelman *et al.*, 1976).

Blood glucose

ASA has been shown to exert a hypoglycaemic effect in both diabetic and non-diabetic individuals (Hecht & Goldner, 1959). Dose regimens of diflunisal as high as 500 mg twice daily did not seem to have any effect on fasting blood glucose levels in normal volunteers (Smit Sibinga *et al.*, 1976) or in diabetic patients receiving tolbutamide concurrently (McMahon & Ryan, unpublished observations).

Special safety studies

General

The most commonly reported adverse experience for nearly all non-steroidal anti-inflammatory/analgesic agents is gastrointestinal irritation (Paulus & Whitehouse, 1973). Most agents of this type, when tested, have been shown to increase the rate of blood loss through the gastrointestinal tract. Additionally, many patients ingesting high doses of ASA often experience tinnitus (Myers *et al.*, 1965). This reversible ototoxicity can occur at or below blood levels of drug normally associated with an optimal therapeutic response.

Gastrointestinal blood loss

Utilizing the standard ^{51}Cr-tagged-red-blood-cell technique, a double-blind, crossover study measuring

gastrointestinal blood loss was carried out to compare diflunisal 500 mg/d with ASA 2.4 g/day. This dose regimen of diflunisal did not cause a statistically significant alteration in the rate of gastrointestinal blood loss (Figure 4); whereas the equianalgesic dose of ASA resulted in a significant increase ($P < 0.01$) in the rate of blood loss from day 2 to day 5 of drug therapy. Note that during the last 2 days of drug treatment the concomitant ingestion of 120 ml 40% ethanol during a 1.5-h period did not cause a significant increase in the rate of blood loss observed with either drug (De Schepper *et al.*, 1975).

Ototoxicity

A special study of aural function was carried out, in which audiometric measurements were made before and 4 d after the initiation of a dose regimen of diflunisal 375 mg every 12 hours. No complaints of tinnitus were registered, nor were any objective signs of ototoxicity detected (Tempero *et al.*, 1975).

Mild tinnitus was reported by four out of 14 subjects who received ASA 600 mg four times daily and diflunisal 250 mg twice daily concomitantly for 3 d (Perrier, unpublished observations). The tinnitus was reversible and no objective signs of ototoxicity could be documented by audiometry. None of the 14 subjects experienced tinnitus when diflunisal 250 mg twice daily was given alone or when a dose regimen of ASA 300 mg four times daily was superimposed on the diflunisal steady state. No tests were made to determine whether the four subjects experiencing tinnitus while taking both ASA 600 mg four times daily and diflunisal 250 mg twice daily would also have experienced tinnitus on a dose regimen of ASA 600 mg four times daily alone. Nevertheless, it is to be expected that some individuals taking both drugs concomitantly, at therapeutic dose levels, might experience tinnitus.

Drug interactions

General

Studies were carried out to determine whether diflunisal had clinically significant interactions with other drugs. Four classes of drugs were investigated: non-steroidal anti-inflammatory/analgesic agents, oral anticoagulants, thiazide diuretics, and oral anti-diabetic drugs.

Non-steroidal anti-inflammatory/analgesic agents

Acetylsalicylic acid. Diflunisal did not influence the absorption or metabolism of single doses of ASA 600 mg (Schulz & Donath, unpublished observations). Data generated by administering dose regimens of ASA 300 mg (single dose and four times daily), 600 mg (single dose and four times daily) along with a diflunisal regimen of 250 mg twice daily, indicated, however, that only the dose regimen of ASA 600 mg four times daily lowered plasma diflunisal levels during 3 d in which the drugs were given concomitantly (Perrier, unpublished observations). The mean drop in the diflunisal plasma level was approximately 15%; although statistically significant, it is not anticipated to have clinical significance.

Indomethacin. The coadministration of diflunisal 250 mg twice daily and indomethacin 25 mg three times daily resulted in an increase of 30–35% in the plasma levels of indomethacin. The clinical importance, if any, of this interaction has not been determined (De Schepper, unpublished observations).

Naproxen. No alterations in naproxen levels in blood and urine were detected when subjects given naproxen 250 mg twice daily also took diflunisal 250 mg twice daily (Dresse, unpublished observations).

Oral anticoagulants

Acenocoumarol (Sintrom®) Three out of six individuals stabilized on oral acenocoumarol, experienced decreases in clotting factors II, VII, and X and increases in prothrombin times — all clinically significant — after beginning a concomitant regimen with diflunisal 375 mg twice daily (Caruso *et al.*, unpublished observations). Therefore, it was concluded that patients receiving both drugs should be followed carefully, in case an acenocoumarol dosage adjustment is necessary after concomitant therapy has been initiated.

Phenprocoumon (Liquamar® and Marcoumar®)
Pilot information obtained by the study of two patients during concomitant administration of therapeutic doses of phenprocoumon and diflunisal 375 mg twice daily indicated that there was no interaction between the two drugs (Vermylen, unpublished observations).

Subsequent *in vitro* binding studies (De Schepper, unpublished observations) with human serum and plasma indicated that therapeutic plasma levels of diflunisal displaced only about 0.1% of protein-bound phenprocoumon. In the same study, therapeutic concentrations of phenylbutazone displaced 10–20 times more phenprocoumon than did the diflunisal.

Thiazide diuretics (hydrochlorothiazide)

Concomitant administration of diflunisal 375 mg twice daily and hydrochlorothiazide 50 mg twice daily caused a 25–30% increase in the plasma levels of hydrochlorothiazide. This increase was probably secondary to a decrease in the renal excretion of

hydrochlorothiazide. This alteration in plasma hydrochlorothiazide levels is not anticipated to be of clinical significance, since neither the incidence of side-effects nor the therapeutic (diuretic and antihypertensive) activity of hydrochlorothiazide increases appreciably when the dose regimen is raised four-fold (McLeod *et al.*, 1970).

The uricosuric activity of this dose regimen of diflunisal completely antagonized the uric acid retention observed during hydrochlorothiazide therapy (Tempero *et al.*, 1976).

Oral antidiabetic agents (tolbutamide)

When patients taking tolbutamide for control of diabetes mellitus added diflunisal 375 mg twice daily to their daily drug intake, no alterations in blood tolbutamide levels or in fasting blood glucose levels were detected (McMahon & Ryan, unpublished observations). It was concluded that no clinically significant drug interaction occurred between these drugs.

Tolerability

During the pharmacokinetic and pharmacodynamic studies 87 subjects and patients received single doses of diflunisal ranging from 50–500 mg, and 70 subjects and patients received multiple dose regimens ranging from 125–500 mg twice daily for periods of 4–7 days. Three out of the 87 people receiving single doses of diflunisal and six of the 70 individuals receiving multiple doses reported mild or moderate adverse experiences which were rated as possibly, probably, or definitely drug related. Seven out of the nine adverse effects (two out of three on single doses and five out of six on multiple doses) were gastrointestinal disturbances: epigastric pain, pyrosis and diarrhoea. The low incidence of adverse experiences during single dose (3%) and multiple dose (9%) regimens indicated that diflunisal was well tolerated.

While taking diflunisal, one subject developed a skin rash which was considered to be definitely drug related. When this subject took an ASA-containing drug at a later date for relief of a headache, a similar skin rash appeared. This was interpreted as evidence of cross sensitivity between diflunisal and ASA.

This paper is a review of 23 studies, and many people were involved in the generation of these data. Therefore, we wish to acknowledge the vital contributions made by the following individuals whose names do not appear among those found in the bibliography: Dr K. Anderson, Dr J.R. Bianchine, Ms A. Buntinx, Dr I. Caruso, Mrs F.D. Deluna, Mr R. DeVries, Dr A. Donath, Dr M. Donati, Mr A.E.W. Duncan, Mrs V. Gruber, Dr K.C. Kwan, Dr R. Latini, Miss L. Leidy, Dr F.G. McMahon, Dr P. Morselli, Dr F. Perret, Ms B. Reger, Dr J.R. Ryan, Dr J. Vermylen, Mr R.W. Walker, Mr P.E. Wittreich and Dr K. Yeh.

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