PROLONGED PLASMA HALF-LIFE AFTER ORAL ISOSORBIDE DINITRATE IN PATIENTS WITH ANGINA PECTORIS

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The plasma concentration of isosorbide dinitrate (ISDN) was monitored up to 24 h after a chronic oral dose of 60 mg in six patients with coronary artery disease. A terminal half-life of 7.7 ± 2.6 h (mean $\pm$ s.d.) was observed. The presence of this prolonged disappearance phase provided at least a partial explanation for the observed accumulation of ISDN in plasma after chronic dosing on a six hourly regimen.

Introduction

In a previous study (Fung *et al.*, 1981b) in which we examined the effects of dose and duration of administration of oral isosorbide dinitrate, ISDN, on its pharmacokinetics and pharmacodynamics in chronic angina patients, we had the opportunity to monitor the plasma ISDN concentrations of one patient for 24 h and observed, quite unexpectedly, the existence of an apparent terminal half-life for the unchanged drug of about 4 h. This observation suggests that the plasma disappearance of ISDN in man might not be as fast as had been generally believed, i.e., 0.5 to 1 h (Laufen *et al.*, 1978; Taylor *et al.*, 1980). The presence of this 'hidden' disappearance phase, if confirmed, could provide a partial explanation for the unusual accumulation kinetics of ISDN observed after chronic dosing (Fung *et al.*, 1981b) and for the appar-

ently longer duration of effect of ISDN that could be accounted for by the reportedly short plasma half-life of this and other organic nitrates.

Methods

Six patients with coronary artery disease were enrolled in a follow-up study to validate this aspect of ISDN kinetics. These individuals have been treated with 60 mg oral ISDN four times daily for periods of 3 weeks to several months. Four individuals in this group were treated with other drugs concomitantly while the remaining two patients were on ISDN alone (Table 1). These patients were admitted to the hospital the day before the study, informed consent was

Table 1 Pharmacokinetic parameters of ISDN in patients receiving 60 mg ISDN orally.

Patient	Other medications	Terminal half-life (h)	$AUC_{0-6}/AUC_{0-\infty}$	CL_0 (l/min)
1*	None	4.3	0.82	6.3
2	Pindolol 5 mg three times daily	8.8	0.51	6.5
3	None	5.8	0.89	6.9
4	None	11.2	1.19	14.0
5	Furosemide 80 mg/day Diazepam 5 mg three times daily	5.2	0.66	4.4
6	Propranolol 80 mg twice daily Ibuprofen 600 mg/day	9.2	0.60	7.1
7	Propranolol 80 mg four times daily Furosemide 40 mg three times daily Naproxen 250 mg three times daily Allopurinol 100 mg three times daily	9.2	1.04	16.1
Mean		7.7	0.82	8.8
s.d		2.6	0.25	4.4

* from previous study (Fung *et al.*, 1981b).

obtained, and a continuing dose of 60 mg was administered at about 08.00 h the following morning, but no subsequent ISDN was administered. Blood samples were drawn at 0, 0.5, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20 and 24 h after dosing. The separated plasma was assayed for ISDN according to a method described previously (Fung *et al.*, 1981b). In two patients, plasma concentrations of the two mononitrate metabolites, isosorbide-2-mononitrate (2-ISMN) and isosorbide-5-mononitrate (5-ISMN) were also determined (Morrison & Fung, 1980). The lower limits of sensitivity of these assays were 0.5 ng/ml and 10 ng/ml for ISDN and its mononitrate metabolites, respectively.

Results and Discussion

Figure 1 (insert) shows the plasma ISDN concentration observed. It is seen that time zero (i.e. some 6–10 h after the last dose was given), significant plasma ISDN concentrations were found (5.3 ± 2.2 ng/ml, mean $\pm$ s.d., $n = 7$). Absorption of ISDN was apparently rapid and peak concentrations of ISDN were observed within 1 h after dosing. The terminal half-life of ISDN, estimated for each patient by linear regression using data from 10 to 24 h, was found to range from 4.3 h to 11.2 h (Table 1). This prolonged half-life was observed in patients receiving ISDN

alone as well as in patients receiving other concomitant therapy (e.g. with β -adrenoceptor blocker or diuretic).

The oral clearance (CL_0) for ISDN was estimated by eq. 1.

$$CL_0 = \frac{\text{Dose}}{AUC_{0-\infty}} \quad \text{eq. 1}$$

where $AUC_{0-\infty}$ is the corrected area under the plasma ISDN concentration vs time curve from time zero to infinity, obtained via eq. 2

$$AUC_{0-\infty} = AUC_{0-24} + \frac{C_{24}}{k} - \frac{C_0}{k} \quad \text{eq. 2}$$

where AUC_{0-24} is the AUC calculated directly from the observed plasma ISDN concentrations from 0 to 24 h, C_{24} and C_0 are the observed ISDN concentrations at 24 and 0 h respectively, and k is the terminal elimination rate constant (0.693 divided by the terminal half-life).

The existence of a prolonged plasma disappearance phase for ISDN reconciles the apparent inconsistency of significant accumulation of drug in plasma with a four times daily dosage regimen (Fung *et al.*, 1981b) even though the 'reported' half-life of approximately 1 h would suggest otherwise. The present data show that if plasma samples were monitored for only 2–4 h after dosing, as was done in some previous studies (Laufen *et al.*, 1978; Taylor *et al.*, 1980), an apparent half-life of 0.5–1 h would have been concluded. The error incurred in the estimation of oral clearance of ISDN could be substantial if an insufficient sampling interval is employed for kinetic studies of ISDN; thus, only $57 \pm 25\%$ and $74 \pm 26\%$ of the total AUC are accounted for when sampling was carried out to 2 and 4 h, respectively. However, if blood samples were monitored for up to 6 h, approximately $82 \pm 25\%$ of the total AUC was accounted for.

Although the physiological basis for this prolonged plasma disappearance phase is not yet certain, an interesting interpretation can be brought out. The *in vitro* degradation half-life of ISDN in human blood at 37°C is about 1.5 h, some five times faster than the average *in vivo* disappearance half-life observed. This would suggest that the terminal decline phase of ISDN is not rate-limited by metabolism or elimination, but by an input process, viz: either re-distribution of ISDN from peripheral tissues back to the systemic circulation, or by exceedingly prolonged absorption of the ingested oral dose. The first of these two possibilities is more probable because this type of 'flip-flop' kinetics has also been observed after intravenous administration of nitroglycerin in rats. (Fung *et al.*, 1981a). Thus, for ISDN decay in human plasma, the first (and faster) half-life likely reflects the process of elimination while the second (and slower) half-life reflects that of tissue re-distribution.

The oral clearance of ISDN determined after

Figure 1 Plasma concentrations of ISDN ($\square$, $\blacksquare$), 2-ISMN ($\blacktriangle$, $\triangle$) and 5-ISMN ($\bullet$, $\circ$) in two patients monitored over 24 h. Insert: Mean $\pm$ s.d. of plasma ISDN concentrations monitored over 24 h in seven patients receiving 60 mg oral ISDN.

chronic dosing at 60 mg (Table 1) is significantly slower ($P < 0.01$) than that previously determined (Fung *et al.*, 1981b) for the same dose after single administration ($CL_0 = 22.1 \pm 8.9$ l/min, mean $\pm$ s.d.). This decrease in oral clearance with chronic ISDN dosing is consistent with that reported earlier (Fung *et al.*, 1981b). A contributing mechanism for this phenomenon might arise from the presence of high circulating levels of mononitrate metabolites after chronic ISDN dosing (Figure 1). These metabolites have been shown to decrease plasma ISDN clearance when they were introduced together with ISDN intravenously in rats (Sutton & Fung, unpublished observation). In the two patients examined for metabolite levels, 2-ISMN and 5-ISMN were shown to have apparent disappearance half-lives of about 3 and 6 h respectively, generally consistent with previous reports (Abshagen *et al.*, 1981; Taylor, 1981).

It is possible that the reduction in apparent oral ISDN clearance after chronic administration may have, in turn, caused (or been contributed by) a reduced production of mononitrate metabolites. Since these metabolites possess some pharmacologic activity, reduced metabolite presence could have contributed, in part, to the diminution of pharmacologic effects observed after chronic dosing (Fung *et al.*, 1981b). The present protocol, however, does not permit a direct comparison between metabolite production after single and chronic ISDN dosing since the absorption and distribution characteristics of ISDN after chronic oral dosing have not been separately defined.

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