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Determination of free propylthiouracil clearance and single sample prediction of steady state

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Propylthiouracil (PTU) has been used in the treatment of hyperthyroidism for many years (Eichelbaum 1976) and is now being evaluated in the treatment of alcoholic liver disease (Orrego et al 1979). Usually, large doses are given at the beginning of treatment of hyperthyroidism and then the dose is reduced as the euthyroid state is achieved (Gilman & Murad 1975). Although the dosage adjustment is made in general, no adjustment is made based on the manner in which individual patients clear the drug. In particular, it would be advantageous in treatment to identify prospectively or retrospectively those individuals who clear the drug so rapidly or so slowly that altered efficacy of standard doses may be expected. A lack of effect of PTU has been observed in some patients as determined by a lack of increase in serum TSH levels (Israel et al 1979). The determination of a full pharmacokinetic profile for every problematic patient would be impractical and so a simpler solution must be sought.

The simplest approach to identifying high clearance patients would seem to be to analyse the drug in urine samples. Unfortunately, only about 1% of the administered dose is excreted unchanged and there is a large degree of interindividual variation (Giles et al 1981). After oral drug administration the pharmacokinetic profile of this drug is particularly uneven (Giles et al 1980; Melander et al 1977) and the determination of high, normal or low clearance patients from a small number of plasma concentrations would have little predictive value.

We have examined the pharmacokinetic profiles of normal subjects and alcoholic liver disease patients after intravenous PTU administration with a view to identifying, as simply as possible, those patients whose drug clearance is above or below the normal range and in whom the administration of standard drug doses may be inappropriate because of reduced or enhanced drug effects.

Materials and methods

All participants in the study gave written consent. The procedure was approved by the joint Ethics Committee on Human Experimentation of the Addiction Research Foundation and the University of Toronto. The 14 healthy, male subjects were aged 27·9 mean with s.d. 4·1 years, the 18 patients in whom alcoholic liver disease had been proved by biopsy (1 female) were aged 50·0 s.d. 8·7 years. The severity of liver disease was assessed by a composite clinical and laboratory index (Orrego et al 1979) and ranged from 1 to 15, with a mean of 5·7, on a scale to 26. All participants had normal renal function.

The parenteral formulation of PTU was prepared as described by Giles et al (1981). The drug (300 mg) was infused over 15 min and plasma samples were obtained at 0, 0·12, 0·25, 0·33, 0·67, 1·2, 1·6, 2·1, 2·8, 3·7, and 6 h. These sampling times were chosen to given approximately equal areas under the curve between any pair of points.

The h.p.l.c. assay and the method used to determine plasma protein binding have been described by Giles et al (1979, 1981).

Each free drug plasma concentration was determined from the product of free fraction at the point and total plasma concentration at that point. Free drug clearance was determined independently of any phrmacokinetic model from dose/area under free curve, extrapolated to infinity.

Results

The free concentration versus time profile of a healthy subject is shown in Fig. 1. The concentrations increase during the 15 min infusion and decline biexponentially thereafter. The healthy subjects had a free fraction in plasma of 17·7 mean with s.d. 1·4% and a free drug clearance of 1454 s.d. 322 ml min^{-1}. As a group, the alcoholic liver disease patients had more variable parameters, they had a free fraction of 22·7 s.d. 5·1% and a free drug clearance of 1668 s.d. 810 ml min^{-1}. Free fraction in

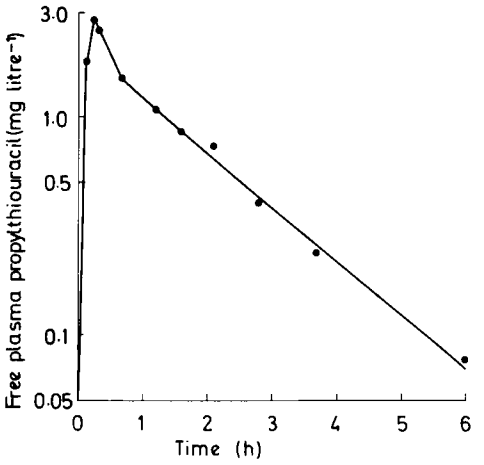

FIG. 1. Free drug concentration versus time profile in a healthy subject. Free drug clearance = 1200 ml min^{-1}.

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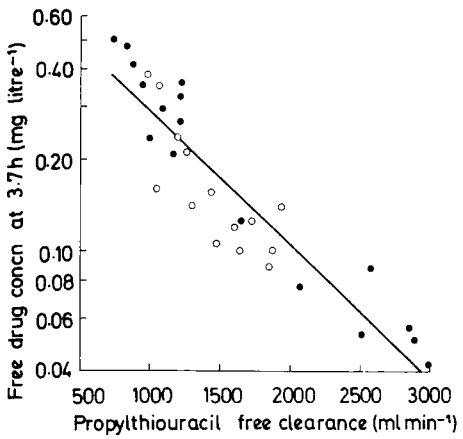

FIG. 2. Correlation (r = 0·92) of free drug clearance and free drug concentration at 3·7 h for normal subjects (open circles) and alcoholic liver disease patients (closed circles).

high free clearance patients (> 2000 ml min^{-1}) was 19·5 s.d. 2·2%. The correlation of free drug clearance and free drug concentration at 3·7 h after infusion is shown in Fig. 2 and accounts for 85% of the variance.

Discussion

Although in this study, PTU was administered as a short infusion, it is simpler to think of it as a bolus. For a 2-compartment open model after an intravenous bolus

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

where C is the free concentration at any time t, A and B are constants, and α and β are hybrid rate constants of the fast and slow disposition phases (Gibaldi & Perrier 1975). PTU is rapidly distributed into a relatively small apparent volume of distribution (Fig. 1) and after distribution equilibrium has been achieved log-linear apparent elimination is observed. Mathematically, this is illustrated by the first exponential term in the equation above approached zero, thus

$$C = Be^{-\beta t} \text{ or } \log C = \log B - \frac{\beta t}{2{\cdot}303}$$

Furthermore, $$\beta \simeq \frac{Cl}{Vd}$$

Where Cl is the free clearance and Vd is the free apparent volume of distribution thus

$$\log C = \log B - \frac{Cl.t}{Vd.2.303}$$

This is a very simple analysis of the pharmacokinetics and while the results are qualitatively correct, criticisms concerning quantitative interpretation have been expressed (Riegelman et al 1968).

A direct relationship, in a group of individuals, between the log of the free concentration and the clearance of free drug depends upon the extent of interindividual variation in the free drug apparent volume of distribution, Vd. Several methods are available to calculate Vd (Gibaldi & Perrier 1975; Kampmann 1977; Giles et al 1981), but none is satisfactory. Some methods are model dependent while in others Vd is merely an empirical parameter. Our data suggests that for PTU interindividual variation in Vd is unimportant compared with the variation of free drug clearance. The negative correlation between the concentration at a fixed time and free drug clearance is excellent, but the distribution of points is not normal. This non-normality reflects the simplicity of the approach but is clearly unimportant in the simple identification of high, normal, and low clearance patients

The same correlation could be done using a sampling time either later or earlier than 3·7 h. At much earlier times, however, distribution equilibrium may not have been achieved for all subjects and the variance will increase. At much later times, the concentration of PTU in samples from high clearance patients will be below the sensitivity of the analytical technique and this would preclude quantitations.

Since the absorption of PTU is virtually complete (Kampmann & Skovsted 1974), knowledge of drug clearance allows the prediction of systemic availability and hence mean steady concentrations during drug administration from

$$\text{Concentration} = \frac{\text{Systemic availability} \times \text{dose}}{\text{Dosing interval} \times \text{clearance}}$$

Similarly, if free drug clearance is known, relative mean steady state free (i.e. pharmacologically active) drug concentrations may be predicted for patients.

It is important to estimate free drug clearance rather than total drug clearance. First, free drug parameters are more likely to be correlated with pharmacodynamics and secondly predictions of free drug clearances from total drug clearance may not always be appropriate. In healthy subjects there is little variation in the plasma protein binding of PTU and the correlation between free and total clearances is excellent (Giles et al 1981). In alcoholic liver disease patients, however, the protein binding is far more variable and this also seems to be true for hyperthyroid patients (Feely et al 1979).

At the present time, optimum mean steady-state concentrations of PTU are not known. It is clear, however, that a dose-response relationship does exist and the delineation of a free concentration-response relationship is a predictable finding in future clinical studies; it has already been found in rats (Francis & Rennert 1980). The approach outlined above allows the efficient determination of an important parameter in drug treatment with minimum patient risk and discomfort.

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The enhancement of dextran anaphylactoid reaction in the rat by sodium salicylate

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Sodium salicylate, like aspirin and indomethacin, is a recognized potent non-steroidal anti-inflammatory agent. However, in animal experiments, it prevents the gastric lesions produced by aspirin without modifying that drug's anti inflammatory effects. It also inhibits the marked gastrointestinal actions of indomethacin, when given either simultaneously (Ezer et al 1976) or up to several hours later (Ezer & Szporny 1981). This protective action of sodium salicylate may be the result of the inhibitory effect of aspirin and indomethacin on prostaglandin synthetase being blocked, as sodium salicylate itself has little effect on that enzyme locally.

Recently, sodium salicylate was found to be an effective adjuvant for the rectal absorption both of insulin and of heparin (Nishihata et al 1981). The enhanced transport of these two drugs across the rectal mucosa is still not understood but the mechanism of action of sodium salicylate appears to be different from that of surfactants like sodium lauryl sulphate which damages the tissue and produces bleeding.

The aim of the present study was to determine the effect of different doses of sodium salicylate on some animal models of inflammation in rats. For example, the dextran anaphylactoid reaction in rats, resulting from the release of histamine and 5-hydroxytryptamine, consists of erythema, pruritus, and gross oedema of the extremities; the reaction mimics many human intolerances to drugs and the early vascular phase of the acute allergic reaction. In the rat it is genetically controlled (Harris et al 1963), just as are many allergic states in man. Doses of sodium salicylate above 100 mg kg^{-1} reduce the reaction (Warne & West 1978), as do aspirin and indomethacin, but the effects of much smaller doses of salicylate have not been studied in detail.

Two types of rat were used—one that responds to the first intraperitoneal injection of dextran (the reactor or R rats obtained from the Tuck Wistar colony) and one that does not (the non reactor or NR rats obtained from the NELP colony). Groups of 5 male animals (250–300 g) were injected with clinical dextran (Intradex, molecular weight 110 000) either intraperitoneally (100 mg kg^{-1}) or locally into a hind paw (50–500 μg). In each case, the percentage increases in hind paw volume were determined on a volume differential meter over 5 h and 60 min, respectively. Each volume shown in the Figures is the mean $\pm$ s.e.m. In other experiments, sodium salicylate was dissolved in 0·9 % NaCl (saline) and administered together with the dextran or 30 min before or after it.

Fig. 1 shows the result for the simultaneous intraperitoneal administration of dextran and sodium salicylate in R rats. The dose of dextran used (100 mg kg^{-1}) was selected so that the anaphylactoid reaction was submaximal. However, the presence of a low dose of sodium salicylate (30 mg kg^{-1}) clearly potentiated the onset of the reaction, the peak value attained, and the duration of the response. The values at all times were significantly raised ($P < 0.05$). This unexpected result suggests enhanced absorption of dextran from the peritoneal cavity (like that reported for insulin and heparin from the rectum). A similar result was obtained when sodium salicylate was injected 30 min after the dextran treatment, but there was no enhancement when it was administered 30 min before. For the dose of dextran used (100 mg kg^{-1}), enhancement was optimal with 30 mg kg^{-1} sodium salicylate, being less with 15 or 60 mg kg^{-1}. NR rats do not produce an anaphylactoid reaction with dextran, and sodium salicylate failed to break down this resistance at all dose levels tested.

When administered locally into one hind paw of R