# PLASMA CONCENTRATIONS OF I.V. PETHIDINE IN HEALTHY VOLUNTEERS UNDER CONDITIONS OF VARIOUS URINARY PH VALUES

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Pethidine has been extensively studied in volunteers and patients. Factors such as urinary pH (Asatoor et al 1963; Chan 1979) liver disease (Klotz et al 1974) age (Chan et al 1975) and physico-chemical properties (Chan 1979) affect the disposition of pethidine. Although urinary pH plays an important part in the renal elimination of the unchanged drug and its weakly basic metabolite, norpethidine; but this effect has not been investigated on the plasma levels of the drug, as most previous studies were carried out under conditions of uncontrolled urinary pH.

In the present communication, this effect on the plasma concentration of pethidine in man is reported. Conditions of uncontrolled and controlled (acidic and alkaline) urinary pH were induced and maintained according to a procedure described previously (Chan 1979). Studies were carried out in 6 volunteer subjects who were fasted overnight. All were healthy Caucasian non-smokers (aged 26-32 years). Each subject was studied on 3 different occasions, separated at least by a period of 7 days. An intravenous cannula was placed in a superficial vein of the subject and kept patent by intermittent infusion of heparinised saline (2ml). Pethidine hydrochloride injection (150 $\mu gkg^{-1}$) was injected intravenously into a vein of the other forearm over a period of not more than 10 seconds. Blood samples (10ml) were collected at 0,2.5,5,10,20,30 and 60 min , and at $1\frac{1}{2}$,2,4,6, 12 and 24 h , into heparinised blood tubes. Plasma samples were removed after centrifugation (2,000g for 15 min ) and stored at -20°C before analysis by a nitrogen-selective gas liquid chromatographic procedure (Tse & Chan 1981). The protocol of these studies was seen and approved by the Medical Research Ethical Committee.

In all subjects, under all 3 conditions of urinary pH, there was a rapid decline in the plasma concentration of pethidine between 2.5 and 10 min. The concentration of the drug then declined more slowly, but was detected in plasma in 4 subjects up to 24 h . In both conditions of uncontrolled and controlled alkaline urinary pH secondary and tertiary peaks appeared during the slow decline phase (20 min to 6 h ); these were not observed under acidic urinary pH (Fig.1). Kinetic analysis indicates that pethidine is eliminated from the plasma triexponentially in all conditions, however, accurate parameters can best be obtained from the acidic urine condition. Average terminal elimination half life $t_{\frac{1}{2}}$ of the drug is 6.1, 7.4 and 8.8 h respectively for conditions of acidic, uncontrolled and alkaline urinary pH. These $t_{\frac{1}{2}}$ are longer than those reported in studies which terminated blood sampling at 6 h post-injection. It is likely that these studies missed the terminal elimination phase which is identified in the present studies.

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Klotz, U. et al (1974) Clin. Pharmacol. Ther., 16: 667-675.
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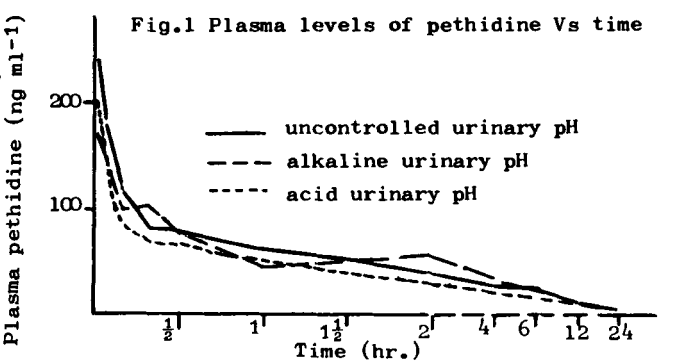
Fig.1 Plasma levels of pethidine Vs time




0022-3573/81/120087P-01$02.50/0