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REGIONAL DISTRIBUTION AND ELIMINATION KINETICS OF IMIPRAMINE IN RAT BRAIN AFTER MULTIPLE DOSAGES

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The elimination of imipramine (IMP) from brain regions was investigated in rats after multiple intraperitoneal (i.p.) administration for 3 weeks. Brain regions could be divided into two classes as to IMP elimination in analogy with a single i.p. dose. IMP levels in the plasma, class A brain regions (cerebellum, mid-brain and medulla, striatum, posterior cortex and frontal cortex) and the initial phase of the curves for class B brain regions (hypothalamus, thalamus, hippocampus and nucleus accumbens) had identical elimination rate constants. They shifted in parallel depending on the dose as in the case of a single dose. On the other hand, the later phase of the curves in the class B brain regions shifted in parallel to the low concentration side with an elimination rate constant similar to that after a single dose. The high-affinity sites for IMP in class B brain regions seemed to be markedly decreased by multiple doses for 3 weeks.

KEYWORDS — imipramine; rat brain region; elimination; distribution; multiple dose; intraperitoneal dose; pharmacokinetics

INTRODUCTION

The tricyclic antidepressant, imipramine (IMP), is widely used in the management of endogenous depression. The pharmacokinetics of IMP and distribution of IMP in the brain have been investigated extensively,[1-7] and the presence of specific high-affinity binding sites for IMP has been demonstrated in the brain by *in vitro* experiments.[8-14] In our recent reports,[15,16] we examined the elimination profile of IMP from certain brain regions after a single intraperitoneal (i.p.) dose in rats and showed that the brain regions can be divided into two classes regarding IMP elimination. Various types of antidepressant drugs are clinically effective only when given over a period of at least a few weeks.[17] In this study, we investigated regional distribution and elimination kinetics of IMP in rat brain after multiple i.p. doses for 3 weeks and showed that there was a difference in the disappearance pattern between the multiple doses and a single dose.

MATERIALS AND METHODS

IMP hydrochloride was obtained from Ciba-Geigy (Japan) Limited (Takarazuka, Japan). All other chemicals were analytical grade products available commercially.

Male Wistar rats weighing 140-150 g at the beginning of the experiment received multiple i.p. doses of IMP (12.5 mg/kg) at 24 h intervals for 3 weeks. Animals were kept under standard laboratory conditions and fed a standard food with free access to water during the experimental period. At various intervals after the last administration (2, 6, 10, 14, 18 and 24 h), the animals were sacrificed. Blood samples were collected in heparinized tubes and the plasma was stored at -30°C. The brain was quickly removed and dissected into 9 regions according to the technique of Glowinski and Iversen.[18] These regions were cerebellum, mid-brain and medulla, hypothalamus, thalamus, striatum, hippocampus, posterior cortex, nucleus accumbens and frontal cortex. After being weighed the brain regions were also stored at -30°C until analyzed. The analytical and pharmacokinetic methods for IMP were described in our previous paper.[15,16]

RESULTS AND DISCUSSION

After the last injection of IMP in rats (12.5 mg/kg i.p. once a day for 3 weeks), the time courses of IMP concentration in plasma and the 9 brain regions, cerebellum, mid-brain and medulla, striatum, posterior cortex, frontal cortex, hypothalamus, thalamus, hippocampus and nucleus accumbens, were studied. The results for plasma, the first 5 brain regions (termed class A) and the last 4 brain regions (termed class B) are shown in Figs. 1, 2 and 3, respectively. Each point represents the mean of 5 animals. The brain regions are divided into two classes as they were in the single-dose studies.[15,16]

Under these experimental conditions, the IMP plasma level (ng/ml) was reduced rapidly following a monoexponential profile with an elimination rate constant of 0.46 h^{-1} (Fig. 1). As shown in Figs. 2 and 3, at 2 h after the administration the IMP concentrations in the brain regions (ng/g wet tissue) were approximately 20-fold higher than the plasma concentration. This indicates a marked accumulation in the brain. However, the ratio of IMP levels in the brain regions to the plasma level was smaller after the multiple dosing than after a single dose. The reason for the reduction is not known, but it may be connected with drug resistance. The answer to this question will be clarified in the near future.

IMP levels in class A brain regions showed monoexponential elimination in a manner similar to the plasma level and the elimination rate constant was 0.42 h^{-1} (Fig. 2). In the single-dose studies[15,16] when different dosages (5 mg/kg and 20 mg/kg) were given, the time courses of IMP levels in plasma and the class A brain regions only shifted in parallel and maintained the same elimination rate constants. The same pattern was followed in the present multiple-dose study when different dosages were given.

The disappearance curves for class B brain regions followed a biexponential profile and could be resolved into two major components as in the single-dose study (Fig. 3). The initial phase (α-phase) of these curves was similar to that in the class A regions and only shifted in parallel, as with the single dose. In contrast, in the later phase (β-phase), IMP was cleared more slowly from class B brain regions with a mean elimination rate constant of 0.16 h^{-1}. This was the

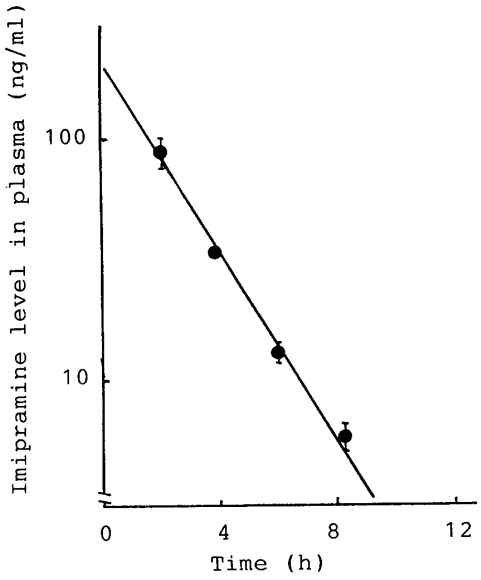

Fig. 1. Time Course of Imipramine Plasma Level (Mean ± S.E.) after Multiple (12.5 mg/kg for 3 Weeks) i.p. Doses of Imipramine

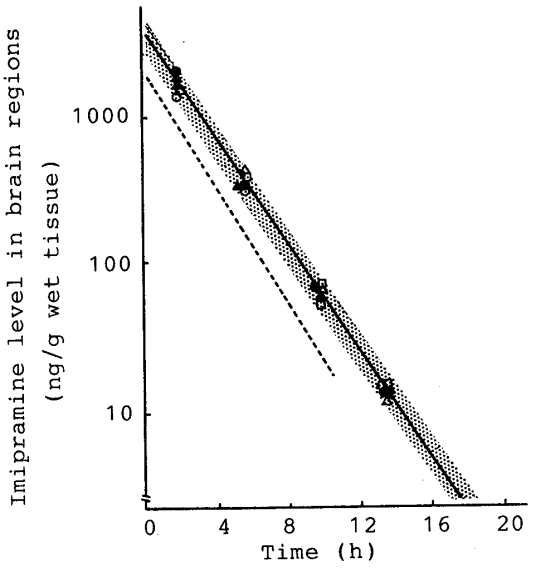

Fig. 2. Time Course of Imipramine Levels Area (Mean ± S.E.) in Class A Brain Regions after Multiple (12.5 mg/kg for 3 Weeks) i.p. Doses of Imipramine
○ , cerebellum; ● , mid-brain and medulla;
△ , striatum; ▲ , posterior cortex;
□ , frontal cortex.
---- after a single (5 mg/kg) i.p. dose of imipramine.[15,16]

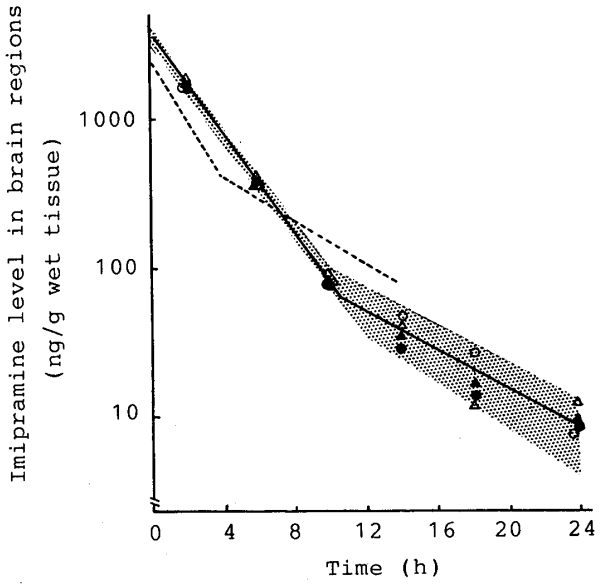

Fig.3. Time Course of Imipramine Levels Area (Mean ± S.E.) in Class B Brain Regions after Multiple (12.5 mg/kg for 3 Weeks) i.p. Doses of Imipramine
○ , hypothalamus; ● , thalamus;
△ , hippocampus; ▲ , nucleus accumbens.
---- after a single (5 mg/kg) i.p. dose of imipramine.[15,16]

same as the elimination rate constant in the β-phase with single doses. On the other hand, the differences between multiple doses and single doses, the IMP levels in the β-phase in class B brain regions shifted in parallel to the low concentration side. With single doses, the IMP levels in the β-phase were not changed by the dose; that is, the initial concentration of the β-phase ($C_{0\beta}$) remained constant at 0.60 μg/g of wet tissue after both the 5 mg/kg and 20 mg/kg single doses. On the other hand, after multiple doses in this study, the initial concentration in the β-phase ($C_{0\beta}$) was 0.22 μg/g of wet tissue. The refraction points appeared 10-12 h and the IMP level was maintained around 10 ng/g of wet tissue even at 24 h after the last administration.

It is interesting that the high-affinity binding site, as indicated in the β-phase in the class B brain regions, was changed by the multiple doses. That is to say, the high-affinity binding site, which was unchanged by the varied single doses, may be changed by multiple doses for 3 weeks. This phenomenon may be related to the pharmacological effect. Also, in in vitro binding experiments, the high-affinity and low-capacity binding sites for IMP in the class B brain regions was decreased by multiple doses for 3 weeks compared with the control[19] (data not shown). The behavior of IMP in vivo in the class B brain regions (Fig. 3) is compatible with the decrease of the high-affinity and low-capacity binding sites in vitro. These phenomena are of interest and further reports are in progress.

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