Pharmacokinetics of Desmethylimipramine and Nortriptyline in Man after Single and Multiple Oral Doses — A Cross-Over Study

B. Alexanderson*
Department of Clinical Pharmacology, University of Linköping, Linköping, Sweden
Received: May 2, 1972

Summary. Eight healthy volunteers received single oral doses (1 mg/kg) and 6 received multiple doses (0.4 mg/kg t.i.d. for 2 weeks) of desmethylimipramine (DMI) and nortriptyline (NT) on different occasions. Kinetic analysis of plasma levels of the drugs showed that the ratios between single-dose peak levels, plasma half-lives and apparent mean "steady-state" plasma levels of the two drugs were constant in all the subjects, and averaged 0.6. Despite their closely related chemical structures the apparent plasma clearance rate of DMI was about twice that of NT, and this might be associated with their different degrees of binding to plasma proteins. — The "steady-state" plasma level of NT in man is known to be genetically determined, and the conformity within each individual of the plasma clearance rates of DMI and NT indicates that the plasma kinetics of both these drugs are controlled by common genetic factors. — The study also shows that the "steady-state" plasma level of DMI, like that of NT, can be predicted accurately from single-dose plasma-level data. Thus, if the kinetic characteristics of one of these drugs in a subject are known, it is possible to predict the plasma kinetics of the other compound.

Key words: Tricyclic antidepressants, desmethylimipramine, nortriptyline, single- and multiple-dose kinetics, plasma concentration, plasma clearance, pharmacogenetics, man.

Prolonged treatment with therapeutic doses of tricyclic antidepressants leads to accumulation of the drug in the body and, after some time, the drug plasma concentration reaches an apparent equilibrium level or "steady-state". Several investigators have shown large variations in "steady-state" plasma concentrations, C_{ss}, between different patients or healthy volunteers receiving approximately the same dose-regime of imipramine (IP) [37, 50], desmethylimipramine (DMI) [24, 25, 26, 27, 42, 49], amitriptyline (AT) [11], and nortriptyline (NT) [3, 25, 26, 42, 51, 52, 53]. Simultaneous treatment with various other drugs may affect the C_{ss} of tricyclic antidepressants [3, 22, 25, 37, 38, 50], but most of the variability in C_{ss} of NT between persons is due to genetic factors [3, 53].

Hammer and Sjöqvist [27] observed that patients who developed high or low plasma concentrations of DMI and NT behaved similarly if their metabolic precursors IP and AT were administered. Later, Hammer et al. [26] found that depressed patients with relatively high C_{ss} of DMI and NT also had prolonged plasma half-lives of oxyphenylbutazone and vice versa. These drugs are mainly metabolized by hydroxylation, they are all extensively bound to plasma proteins and only small amounts are excreted unchanged in the urine [26]. It was suggested that DMI, NT and oxyphenylbutazone were metabolized by a common non-specific enzyme system, but the possible effects of previous drug-exposure could not be excluded (loc. cit.).

In a cross-over study of volunteers Vesell et al. found a correlation between the single-dose half-lives in plasma of dicoumarol and phenylbutazone [45]. Both dicoumarol and phenylbutazone are known to be extensively bound to plasma albumin, and it seemed possible, therefore, that their half-lives were determined not so much by their rate of metabolism as by their rate of release from plasma protein binding [33]. After five daily doses the plasma half-lives of phenylbutazone and oxyphenylbutazone correlated well with those of antipyrine in the same subjects [16]. The single-dose plasma half-lives of NT and oxazepam were studied in 12 healthy volunteers but no correlation was found between their plasma kinetics [46].

It has recently been proposed from single- and multiple-dose studies of NT in six healthy volunteers [1, 4] that, besides interindividual differences in plasma half-lives, there might be variations in the apparent volume of distribution of NT as well. The same volunteers have now participated in a similar single- and multiple oral dose-study of DMI which is described in the present paper.

The purpose of the experiments with DMI and

* Licentiate in Medicine, Research Assistant in Clinical Pharmacology.
NT was 1. to investigate the relationships between various pharmacokinetic parameters observed during different dose-regimens in non drug-exposed healthy subjects; and 2. to discover whether inter-subject variations in $C_{eq}$ of DMI could possibly be ascribed to the same genetic factors that control the "equilibrium" levels of NT in man.

**Materials and Methods**

**Subjects and drug administration**

Eight members of our research staff, 3 females and 5 males, received a single oral dose of DMI-hydrochloride (1 mg/kg). This was always taken in the morning after overnight fasting and food was withheld for at least 4 h after drug administration. One month later the same people were given DMI-hydrochloride orally in doses of 0.4 mg/kg every 8 h for 2 weeks; one subject (O.B.) received this treatment for only 10 days.

The volunteers were considered healthy as judged by history, physical examination, electrocardiogram and routine laboratory analyses, including hemogram, sedimentation rate, and urine screening for protein, glucose and bacteria. Details of their ages, sex and weights are given in Table 1.

**Plasma specimen collections**

Prior to the administration of single doses of DMI and NT, a blood specimen was drawn to provide a plasma blank. Eight to 12 blood samples were then collected at different time points during the next 60 to 100 h.

During treatment with DMI and NT the changing plasma levels were estimated in from 7 to 11 blood specimens, which always were taken about one hour before the afternoon dose, i.e. at 2 p.m. The decline of plasma concentrations from the "steady-state" values were determined in 6 to 9 blood samples obtained during the 60 to 100 h following the last dose of the drug-DMI on day 153, and NT on day 143.

**Analysis of DMI and NT in plasma**

Blood samples were collected in heparinized tubes and immediately centrifuged at 650 g for 10 min. Six ml of plasma was removed and mixed with 1.5 ml 0.1 N HCl. The samples were stored in a freezer until assayed according to Hammer and Brodies method [24], as further described by Sjöqvist et al. [42]. The total concentrations of DMI and NT in plasma were determined in terms of their free bases. The majority of samples were processed in triplicate.

**Theoretical Pharmacokinetics**

**Single dose kinetics**

The overall plasma half-lives ($t_{1/2}$) of DMI and NT, and their corresponding elimination rate constants, $\beta$, were estimated by the least squares method from the last apparently monoexponential parts of the log plasma concentration ($C$) against time ($t$) curves. The relationship between the biological plasma half-life, $t_{1/2}$, of a drug and its elimination rate constant, $\beta$, is given in Eq. 1:

$$t_{1/2} = \frac{0.693}{\beta} \quad \text{Eq. 1.}$$

The apparent volume of distribution of a drug, determined as $(Vd)_A$, relates the total amount of drug in the body to the drug concentration in plasma at all times during the terminal exponential phase, i.e. the $\beta$-slope [19]. $(Vd)_A$ was estimated from Eq. 2 assuming complete availability ($f = 1$) of given doses, $D$:

$$\frac{(Vd)_A}{\beta} = \int_0^\infty \frac{C(t)dt}{\beta} \quad \text{Eq. 2.}$$

where $\int_0^\infty C(t)dt$ is the area under the plasma concentration curve from zero to infinite time. This area was calculated partly by the trapezoidal rule from

---

**Table 1. Subjects participating in the single and multiple dose studies of DMI and NT**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>DMI Age yrs</th>
<th>Weight kg</th>
<th>NT Age yrs</th>
<th>Weight kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. A.</td>
<td>M</td>
<td>28</td>
<td>80</td>
<td>27</td>
<td>79</td>
</tr>
<tr>
<td>G. A.</td>
<td>M</td>
<td>26</td>
<td>85</td>
<td>25</td>
<td>83</td>
</tr>
<tr>
<td>I. B.</td>
<td>F</td>
<td>31</td>
<td>51</td>
<td>38</td>
<td>50</td>
</tr>
<tr>
<td>O. B.</td>
<td>M</td>
<td>31</td>
<td>63</td>
<td>30</td>
<td>61</td>
</tr>
<tr>
<td>M. G.</td>
<td>M</td>
<td>23</td>
<td>66</td>
<td>22</td>
<td>67</td>
</tr>
<tr>
<td>M. L.</td>
<td>F</td>
<td>32</td>
<td>69</td>
<td>31</td>
<td>67</td>
</tr>
<tr>
<td>A. R.</td>
<td>M</td>
<td>27</td>
<td>80</td>
<td>26</td>
<td>80</td>
</tr>
<tr>
<td>M. A.</td>
<td>F</td>
<td>32</td>
<td>54</td>
<td>31</td>
<td>59</td>
</tr>
</tbody>
</table>

*a These subjects did not take part in the multiple-dose NT-study.

The drug was dispensed at the Military Pharmacy, Karolinska Hospital in Stockholm. All capsules were weighed to an accuracy of ± 1 mg. No excipient was added to the capsules.

Six of the subjects had previously participated in a similar study of NT-hydrochloride and two of them (I. B. and M. A.) only took part in the single-dose test of NT. None had been treated with drugs between the two studies.

---

2 On day 9 in subject O.B.

3 On day 13 in subject M.G.