The redistribution of selected psychiatric drugs in post-mortem cases

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Abstract

The post-mortem redistribution of a number of psychiatric drugs was investigated. A portion of liver, the gastric contents and blood collected from heart and femoral sites was obtained from 13 cases and analyzed by liquid chromatography–mass spectrometry. Drugs detected included five selective serotonin reuptake inhibitors; venlafaxine, a serotonin/noradrenaline reuptake inhibitor; and risperidone, an atypical antipsychotic. Heart blood concentrations were significantly higher (3.4-fold on average) than those measured in femoral blood when results from all drugs were included together. The range for parent drug concentrations in these two blood specimens was 0.5–6.2. There was no significant correlation of the post-mortem interval, the liver concentration and content of drugs in the gastric contents to the heart:femoral blood concentration ratio. These data serve to demonstrate that variable increases in blood concentration occur post-mortem and limit the interpretative value of such toxicological data.

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1. Introduction

Post-mortem redistribution, in which drug concentrations in blood specimens from various areas of the body change during the post-mortem interval, has been observed for many drugs. This is believed to occur largely through diffusion from a high to a low concentration and is believed to be time dependent. The extent to which a drug undergoes post-mortem redistribution is also dependent on protein binding and lipophilicity. Drugs with high volumes of distribution, i.e. greater than 3 L/kg, are thus more prone to post-mortem redistribution [1–3]. Diffusion of drug from the gastrointestinal tract into neighboring tissues has also been shown to contribute to redistribution [2,4,5]. An understanding of post-mortem tissue distribution is therefore important to determine the role of these drugs in the death process.

Tissue distribution of several serotonin reuptake inhibitors (SSRI) and atypical antidepressants has been studied [6–13]. In many cases, only one blood sample was taken, so it was impossible to determine if redistribution had actually occurred. In cases where both central and peripheral blood specimens were taken, no significant difference was seen for sertraline [8,11]. However, slight differences in paroxetine and fluoxetine concentrations were observed in central versus peripheral blood in one case of a subject who died in hospital [13], but neither drug was present on admission. It was suggested that the drugs were administered in hospital and the differences in concentration between the two specimens were most likely a result of incomplete absorption. In the two studies in which post-mortem peripheral and central blood venlafaxine and metabolite concentrations were compared, central blood concentrations were approximately 1.5–2 times those found in peripheral blood [8,9,12].

These studies do not allow a definitive conclusion to be made regarding redistribution of antidepressant drugs in general, or even many of the individual drugs already discussed. However, the uneven tissue distribution patterns often observed for these drugs, combined with their relatively high volumes of distribution (up to 28 L/kg), significant protein binding (0.27–0.99) and relatively high lipophilicity (log P = 2.9–5.4) suggest that post-mortem redistribution is very likely. We have assessed the degree of redistribution of selected psychiatric drugs by analyzing blood specimens collected from heart and femoral sites. Since the possibility exists for drugs in the stomach contents to diffuse into the liver or centrally collected blood, this heart:femoral blood concentration ratios were compared to drug concentrations measured in liver and stomach contents.
2. Materials and methods

2.1. Specimen collection

Cases were selected based on circumstances where one or more of the target drugs were likely to have been used by deceased. Matched post-mortem femoral and heart post-mortem blood specimens were collected in 10 mL plastic tubes containing preservative (1% sodium fluoride and potassium oxalate) and were stored at −20°C until assay. Specimens were classified according to their consistency (i.e. thin or watery looking or viscous) and color.

2.2. Specimen preparation

All cases were subject to a full toxicological examination for the presence of range of common drugs. When drugs were detected these were confirmed by standard GC–MS techniques. For quantification purposes parent drugs and where relevant metabolite concentrations were measured. The extraction technique used was performed based on a procedure described by McIntyre et al. [14] and modified for use with LC–MS as described previously using trazodone as internal standard [15,16].

2.3. LC–MS conditions

LC–MS analysis was performed on a 1100 Series HPLC (Agilent Technologies, Forest Hill, Vic., Australia) configured with a G1946A mass selective detector (MSD). It was operated in positive mode APES as described previously [15]. For quantification purposes, mass spectral detection was conducted in the SIM mode.

2.4. Post-mortem intervals (PMI)

The time of death, time of admission to the Institute and time of autopsy were recorded for each case included in this study. The post-mortem interval was the estimated time between death and autopsy. In cases where the time of death was unknown, the time of death was taken as the half-way point between when the subject had last been seen alive and when he or she was found dead.

2.5. Statistical analyses

Statistical evaluation of the data was performed using SigmaStat 2.03 (SPSS Inc.) and software on an IBM personal computer. Kruskal–Wallis one-way ANOVA at the 95% confidence interval were used to determine whether differences between heart and femoral blood concentrations were statistically significant. Pearson correlations were used to determine statistical significance of correlations between heart:femoral blood concentration ratios and each of the following pharmacokinetic parameters: volume of distribution ($V_d$), protein binding ($F_b$) and lipophilicity (log $P$). Values for log $P$ were calculated using PALLAS Expert System V3.0 software [17].

2.6. Ethics review process

Ethics approval for the use of these specimens for the purposes of research was obtained through the Institute’s Ethical Review Committee and informed consent was obtained from the senior next of kin.

3. Results

3.1. Effect of PMI and redistribution

A total of 13 cases were investigated. The PMI was $64 \pm 17$ h (range 42–90). In seven cases the exact time of death was known. There was no significant relationship between the PMI and the heart:femoral blood concentration ratio (Table 1).

3.2. Comparison of site of sampling and redistribution

The concentrations of drugs and their metabolites were compared in all 13 matched autopsy femoral and heart blood specimens (Table 1). Overall, differences in blood concentrations between the two sampling sites was statistically significant (non-parametric ANOVA, $p < 0.05$). The average heart:femoral blood concentration ratio was 3.4, although there was substantial variability within and between drugs. Heart:femoral blood concentration ratios ranged from 0.50 to 6.2, although they averaged between 2–3:1. With the exception of norfluoxetine in case 2, the mean metabolite concentration ratios were similar to those of their parent drugs. In cases 4, 5 and 12, the heart blood specimen was noticeably lighter in color and therefore thinner than its corresponding femoral blood specimen. Cases 4, 5 and 12 accounted for the highest heart:femoral blood concentration ratios.

3.3. Redistribution from the gastrointestinal tract

Stomach contents were collected and assayed for drug residues in seven cases. Absolute amounts in the positive cases ranged from 0.05 to 2.0 mg. These values were all below the amount of drug contained in one standard tablet. With the exception of cases 2 and 4, the heart blood concentrations were not much higher than those in femoral including those cases for which drug residues were detected in the gastric contents.

3.4. Redistribution from the liver

Liver specimens were collected and analyzed for drug concentrations in 10 cases. Liver drug concentrations ranged from about 0.02 to 13 mg/kg. There was no significant difference in heart blood concentration ratio as a function of liver concentration when liver concentrations were dichotomized to less than and greater than or equal to 1 mg/kg (Table 1).
3.5. Effect of physiochemical properties and extend of redistribution

No significant correlation was observed between concentration ratios and any of the known physiochemical parameters specified in Table 2. There was also no significant difference in the result if drugs were categorized according to drug type (SSRI, SNARI and antipsychotic) or results for all drugs were tested together in one group. If results from previously published studies were also included, correlations still did not reach significance [8–13,18–21].

4. Discussion

Individual heart:femoral concentration ratios greater than two were observed with fluoxetine, paroxetine, sertraline, venlafaxine and risperidone, however these were quite variable even for those drugs for which there was more than one case example. For example, the two sertraline cases had ratios of 4.8 and 1.0 and for the four venlafaxine cases the ratios ranged from 1.0 to 5.5. Previous studies on citalopram and venlafaxine have found higher heart:femoral concentration ratios, more in line with that measured in case 5 [9,12,20]. However, the citalopram, venlafaxine and O-desmethylvenlafaxine concentrations measured in other studies were not particularly different to those measured in the presented cases for either parent drug or metabolite.

The findings in this study are consistent with both the higher volumes of distribution and protein binding for citalopram and venlafaxine compared to the other drugs. The heart:femoral concentration ratio of O-desmethylvenlafaxine was slightly higher than that of venlafaxine (1.5:1 compared to 1.1:1). The difference in ratios between the presented results and those of other studies may be attributable to differences in parent drug:metabolite ratios. Jaffe found venlafaxine exhibited significant post-mortem redistribution, evidenced by an average autopsy:admission blood concentration ratio of

Table 1
Drug concentrations of selected psychiatric drugs in post-mortem heart and femoral blood and liver specimens in 13 cases and their corresponding heart:femoral ratio

<table>
<thead>
<tr>
<th>Drug</th>
<th>Case no.</th>
<th>PMI (h)</th>
<th>Heart concentration (mg/L)</th>
<th>Femoral concentration (mg/L)</th>
<th>Heart:femoral ratio</th>
<th>Liver concentration (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>2</td>
<td>43</td>
<td>0.93</td>
<td>0.15</td>
<td>6.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Norfluoxetine</td>
<td>2</td>
<td>43</td>
<td>1.33</td>
<td>0.16</td>
<td>33</td>
<td>2.4</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>3</td>
<td>46</td>
<td>0.59</td>
<td>0.75</td>
<td>0.79</td>
<td>12</td>
</tr>
<tr>
<td>Sertraline</td>
<td>6</td>
<td>53</td>
<td>0.36</td>
<td>0.24</td>
<td>4.8</td>
<td>n.t.</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>76</td>
<td>0.05</td>
<td>0.05</td>
<td>1.0</td>
<td>3.3</td>
</tr>
<tr>
<td>N-Desmethyl sertraline</td>
<td>6</td>
<td>53</td>
<td>0.93</td>
<td>0.42</td>
<td>2.2</td>
<td>n.t.</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>76</td>
<td>0.26</td>
<td>0.34</td>
<td>0.76</td>
<td>13</td>
</tr>
<tr>
<td>Citalopram</td>
<td>7</td>
<td>57</td>
<td>1.8</td>
<td>1.6</td>
<td>1.1</td>
<td>n.t.</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>12</td>
<td>83</td>
<td>3.2</td>
<td>0.73</td>
<td>4.4</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>90</td>
<td>0.49</td>
<td>0.44</td>
<td>1.1</td>
<td>n.t.</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>5</td>
<td>52</td>
<td>0.28</td>
<td>0.19</td>
<td>5.5</td>
<td>n.d.</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>77</td>
<td>0.72</td>
<td>0.80</td>
<td>0.90</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>79</td>
<td>0.05</td>
<td>0.05</td>
<td>1.0</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>80</td>
<td>1.1</td>
<td>1.1</td>
<td>1.0</td>
<td>0.85</td>
</tr>
<tr>
<td>O-Desmethyl-venlafaxine</td>
<td>5</td>
<td>52</td>
<td>0.61</td>
<td>0.76</td>
<td>0.80</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>77</td>
<td>1.0</td>
<td>1.1</td>
<td>0.91</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>79</td>
<td>0.78</td>
<td>0.30</td>
<td>2.6</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>80</td>
<td>1.4</td>
<td>0.92</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1</td>
<td>42</td>
<td>0.01</td>
<td>0.02</td>
<td>0.50</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>50</td>
<td>1.8</td>
<td>0.36</td>
<td>5.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>76</td>
<td>0.33</td>
<td>0.22</td>
<td>1.5</td>
<td>0.22</td>
</tr>
<tr>
<td>9-OH-risperidone</td>
<td>1</td>
<td>42</td>
<td>0.01</td>
<td>0.008</td>
<td>1.3</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>50</td>
<td>0.18</td>
<td>0.09</td>
<td>2.0</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>76</td>
<td>0.50</td>
<td>0.25</td>
<td>2.0</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

N.d.: not detected, n.t.: no liver tissue available, PMI: post-mortem interval.

Table 2
Volumes of distribution (Vd), %protein bound (Fb) and lipophilicity (log P) values for drugs under investigation

<table>
<thead>
<tr>
<th>Compound</th>
<th>Vd (L/kg)</th>
<th>Fb</th>
<th>log P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>15</td>
<td>0.80</td>
<td>3.7</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>26</td>
<td>0.94</td>
<td>4.7</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>25</td>
<td>0.77</td>
<td>3.1</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>16</td>
<td>0.95</td>
<td>3.6</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1.2</td>
<td>~0.90</td>
<td>3.3</td>
</tr>
<tr>
<td>Sertraline</td>
<td>25</td>
<td>0.99</td>
<td>5.4</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>8</td>
<td>0.27</td>
<td>2.9</td>
</tr>
</tbody>
</table>

*Log P values calculated using Pallas 3.0 software from CompuDrug [17].
abdominal blood vessels post-mortem. This would result in an increase in drug concentrations during the post-mortem interval [25]. Similarly, diffusion from the GIT has been shown to increase drug concentration in the liver in animal [25], and human cadaveric models [5]. In the cases presented here there was no apparent correlation observed between heart to femoral blood concentration ratio with either liver concentration or gastric contents of drugs.

No significant correlation was observed between concentration ratios and any of the known physiochemical parameters specified in Table 2. There was no significant difference in the result if drugs were categorized according to drug type (SSRI, SNARI and antipsychotic) or results for all drugs were tested together in one group.

The lack of any apparent correlation of any of the physiochemical parameters and the extent of heart to femoral blood concentration ratio does suggest that differences in the heart and femoral blood concentration reflects a number of processes that are either still unknown or, more likely, that these are factors are sufficiently variable as to not be predictable.

A significant weakness in our study was the absence of a specimen earlier than that taken at post-mortem. Earlier sampling was not possible due to legal and ethical restraints. It is conceivable that redistribution of whatever mechanism(s) occurs within the first several hours and that by 1–3 days even the femoral blood has become sufficiently elevated as to not be particularly useful [23]. It is also worth noting that even drugs in femoral blood will also be affected by redistribution (and other) processes. The collection of femoral blood reduces the extent of the changes but does not negate the changes.

This variability in heart and femoral blood concentrations suggests that blood concentration variations between heart and femoral blood are too variable to be predictive and allow some degree of certainty over possible estimates of peri-mortem blood concentrations. Nevertheless, these data reassert the need to ensure the site of blood collection is specified.

While more data are needed to understand the complex changes in drug concentration occurring after death these data serve to demonstrate again that post-mortem redistribution is a variable phenomenon and plays a major limiting factor in any interpretation of post-mortem drug concentration in blood.

Acknowledgements

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References


2.5:1 [8] (see Table 3). This finding is not surprising in light of the comparatively high volume of distribution of this drug. In contrast, fluvoxamine showed ratios somewhat lower to that reported elsewhere [21]. This also occurred for sertraline [10,11] (see Table 3). The heart:femoral concentration ratios of the metabolites norfluoxetine and 9-OH-risperidone generally reflected those of their parent drugs.

Studies have shown arterial–venous differences in drug concentrations during the drug absorption and distribution phase [3]. Therefore, if a person dies while a drug is still being distributed throughout the body, toxicological results may vary more and will less likely to be predicted than when absorption was complete. This may explain the lower heart:femoral ratios observed in my data for case 3. Since fluvoxamine acid metabolite concentrations were not measured in this case, it is not possible to make conclusions regarding the extent of ante-mortem drug absorption or distribution.

A study of post-mortem redistribution of paroxetine in the rat showed that increases in drug concentrations in post-mortem blood were accompanied by decreased drug concentrations in the lung over the post-mortem interval [22]. Similar conclusions were obtained using citalopram in the rat [23]. This was also observed in dog studies in which decreases in lung and liver concentrations of fluoxetine were accompanied by increases in heart blood concentrations over time [24].

It has also been suggested that in some cases of drug overdose, a certain amount of unabsorbed drug remains in the stomach and gastrointestinal tract (GIT), which can diffuse into


