Recent media coverage has raised awareness of the involvement of drugs, both licit and illicit, in the crime of 'date' or 'acquaintance' rape. The term 'date rape drug' has been coined and has been used to label a few specific drugs because of their alleged properties. These include flunitrazepam (Rohypnol), gamma hydroxybutyrate (GHB) and ketamine. Concerns over reports of flunitrazepam in connection with 'date rape' led to action by the manufacturer of Rohypnol (flunitrazepam), F. Hoffman-La Roche Ltd. who undertook an educational campaign warning of the dangers of drug-assisted sexual assault, and changed their drug's formulation internationally to prevent its clandestine use. Despite the media interest, there has been little evidence and no systematic investigation to date of the incidence of drug use in the crime of sexual assault. The present study, from the USA, was therefore instigated to assess the extent to which different drugs were present in the urinalysis of samples supplied by victims of rape where drugs were allegedly involved. The study was so designed as to examine any changes over time in the patterns of drug use in sexual assault. Between June 1996 and May 1998, 1033 samples were tested. Nearly 20 different substances were detected among the 611 specimens that tested positive. Of these, 382 (37 per cent of all specimens) were positive for alcohol and 191 (18.5 per cent) were positive for cannabinoids. GHB was detected in 4.4 per cent of samples. Only six (<0.6 per cent) specimens showed evidence of flunitrazepam, and four of those contained other substances including cocaine, alcohol and/or morphine. Thus, only 0.2 per cent of all samples were positive for flunitrazepam alone. These data clearly indicate that there is no evidence of widespread misuse of flunitrazepam in sexual assault. Alcohol remains the substance most frequently associated with this type of crime. Copyright © 1999 John Wiley & Sons, Ltd.

KEY WORDS — flunitrazepam; Rohypnol; benzodiazepine; alcohol; date rape; acquaintance rape; sexual assault

INTRODUCTION
Recent media coverage has raised awareness of the issue of drugs in the crime of 'date' or 'acquaintance' rape (Frintner and Rubinson, 1993; Koss et al, 1998; Masters, 1997; Peipert and Domagalski, 1994). The term 'date rape drug' has been coined to refer to substances used to intoxicate or incapacitate potential victims, rendering them more vulnerable to sexual assault and less able to remember details of the events surrounding the crime. The label has been applied to certain specific substances because of their alleged properties. These include the benzodiazepine, flunitrazepam (Rohypnol) (Ansell et al, 1997; Simmons and Cupp, 1998; Woods and Winger, 1997); gamma hydroxybutyrate (GHB) (Masters, 1997; Anonymous, 1997); and ketamine, a general anaesthetic (Martin, 1997).

Flunitrazepam was introduced in 1975. Since then, it has been marketed in over 80 countries, and some 250 million courses of treatment have been prescribed. Flunitrazepam is indicated for the treatment of insomnia and as an anaesthetic premedication. Although differences in potency between flunitrazepam and diazepam have been reported in a misleading way by certain media, the 1 mg tablets of flunitrazepam are clinically equivalent to diazepam, 10 mg (Heinzl and Hossli, 1978; Mattila and Larni, 1980).

The hypnotic effect of flunitrazepam is more powerful than its anxiolytic, muscle-relaxant and anticonvulsant actions (Hindmarch, 1977, 1990). Sedation occurs about 20–30 min after a therapeutic (oral) dose of 1–2 mg, peaks within 1–2 h
and may persist for 6–8 h (Hindmarch et al., 1977; Mattila and Larni, 1980), thought it has few residual effects once the period of sleep has passed (Hindmarch, 1990; Harrison et al., 1985). Flunitrazepam may be particularly appropriate for sleep at unusual times (Nicholson et al., 1980).

As with other benzodiazepines, flunitrazepam causes anterograde amnesia — this is considered to be an advantage in its use as a preoperative medication (Hindmarch, 1990; Subhan and Hindmarch, 1984). The combination of benzodiazepines, including flunitrazepam, with alcohol can lead to profound sedation and anterograde amnesia (Hindmarch, 1990; Subhan and Hindmarch, 1983).

Concerns over reports of flunitrazepam in connection with ‘date rape’ led the manufacturer of Rohypnol (flunitrazepam) to undertake an educational campaign in the USA warning of the dangers of drug-assisted sexual assault. Hoffmann-La Roche Ltd. has reformulated its 1 mg tablet to change the shape, colour, coating, marking and packaging to deter any illicit misuse of the drug, whilst maintaining safety and efficacy for legitimate patients. Following reports of the potential for this and many other drugs and substances to be used in sexual assault, Roche has added a dye to the tablet which releases a bright blue colour as it dissolves in liquid. The new tablet is strongly coloured and dissolves more slowly than the old formulation. These changes and the blue colour make it more easy to detect if it should be covertly put into someone’s drink. As of December 1998, 21 countries, including Colombia, Argentina and Mexico, from which there are concerns that illegal trafficking of flunitrazepam to the USA has occurred, had approved the new formulation.

Despite the widespread media interest, there has been little proven evidence and no systematic investigation of the incidence of drug use in the crime of sexual assault (Saum and Inciardi, 1997; Calhoun et al., 1996). A study was therefore instigated in the USA to assess the extent to which alcohol and other drugs were present in sexual assault. Roche has added a dye to the tablet which releases a bright blue colour as it dissolves in liquid. The new tablet is strongly coloured and dissolves more slowly than the old formulation. These changes and the blue colour make it more easy to detect if it should be covertly put into someone’s drink. As of December 1998, 21 countries, including Colombia, Argentina and Mexico, from which there are concerns that illegal trafficking of flunitrazepam to the USA has occurred, had approved the new formulation.

Despite the widespread media interest, there has been little proven evidence and no systematic investigation of the incidence of drug use in the crime of sexual assault (Saum and Inciardi, 1997; Calhoun et al., 1996). A study was therefore instigated in the USA to assess the extent to which alcohol and other drugs were present in samples taken from victims of rape where substances were allegedly involved (ElSohly and Salamone, submitted).

**METHOD**

ElSohly Laboratories, an independent, US Government-certified forensic toxicology laboratory, has set up a testing facility (Ledray, 1997) available in the USA to law enforcement agencies, hospital emergency departments and rape crisis centres involved in the investigation of sexual assaults in which misuse of a drug was alleged. The present report describes the currently available results of this ongoing programme, which is funded by Roche Laboratories. Urine samples were collected over a period of 24 months, from June 1996 to May 1998, as described by ElSohly and Salamone (submitted). This period was arbitrarily divided into an initial phase (June 1996–July 1997) and a secondary phase (August 1997–May 1998) to facilitate the identification of trends in the pattern of drug use in sexual assault.

The samples were tested by OnLine immunoassay (Crouch et al., 1998; Salamone et al., 1997; ElSohly and Salamone, submitted) for the presence of amphetamines, barbiturates, benzodiazepines (50 ng/ml cut-off), benzoylecgonine, cannabinoids, methaqualone, opiates, phencyclidine and propoxyphene. Positive results were confirmed by gas chromatography–mass spectrometry (GC–MS). The samples were also tested for gamma hydroxybutyrate by GC–MS and for alcohol by gas chromatography–flame ionization detection. Ketamine was not included in the analysis because intoxication with this drug is easily identifiable.

Flunitrazepam can be difficult to detect in urine samples. Because of its potency, it is administered in doses that are relatively small compared to other benzodiazepines. However, a recently developed method (ElSohly et al., 1997; ElSohly and Salamone, submitted; Valentine et al., 1996) is able to detect low concentrations of 7-amino-flunitrazepam, the major urinary metabolite of flunitrazepam. The technique uses a highly specific and sensitive GC–MS analysis which has a detection limit of less than 1 ng/ml. This procedure can confirm the presence of flunitrazepam metabolites in urine at least 72 h after ingestion of a 1 mg dose of the drug (ElSohly et al., 1997; Salamone et al., 1997).

Samples were submitted with anonymous case-record forms which recorded the place and time of the assault and when the sample was taken (ElSohly and Salamone, submitted).

**RESULTS**

During the initial phase, 388 samples were submitted for analysis; these were followed by a further 645 in the secondary phase, making a total of 1033 samples. Additionally, 11 samples could not be
analysed as the specimens leaked in transit. Table 1 gives the cumulative totals of the test results for these samples by drug. Note that these figures relate to the number of positive and negative tests, rather than samples (123 samples were positive for more than one drug). Composite figures for stimulants (amphetamines and cocaine), CNS depressants (ethanol, barbiturates, GHB and benzodiazepines, including flunitrazepam), and illicit drugs (GHB, cannabinoids, opiates, cocaine, and amphetamines) are provided in Table 2. Again, these figures relate to the number of positive tests as some samples were positive for more than one drug. Table 3 summarizes the sample set, giving the total numbers of positive and negative samples and the total numbers of positive tests.

To identify trends in the data, a growth factor was calculated for each of the drugs by dividing the number of positive tests at the end of the second period by those at the end of the first phase. When

### Table 1. Urinalysis results for the two phases of the study, by drug.

<table>
<thead>
<tr>
<th>Drug</th>
<th>First phase</th>
<th>Second phase</th>
<th>Growth factor</th>
<th>Index of change</th>
</tr>
</thead>
<tbody>
<tr>
<td>None found</td>
<td>138</td>
<td>422</td>
<td>3.06</td>
<td>1.15</td>
</tr>
<tr>
<td>Non-flu BZ</td>
<td>59</td>
<td>129</td>
<td>2.19</td>
<td>0.82</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>4</td>
<td>6</td>
<td>1.50</td>
<td>0.56</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>3</td>
<td>10</td>
<td>3.33</td>
<td>1.25</td>
</tr>
<tr>
<td>Ethanol</td>
<td>113</td>
<td>382</td>
<td>3.38</td>
<td>1.27</td>
</tr>
<tr>
<td>GHB</td>
<td>30</td>
<td>45</td>
<td>1.50</td>
<td>0.56</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>49</td>
<td>191</td>
<td>3.90</td>
<td>1.46</td>
</tr>
<tr>
<td>Opiates</td>
<td>16</td>
<td>37</td>
<td>2.31</td>
<td>0.87</td>
</tr>
<tr>
<td>Codeine</td>
<td>10</td>
<td>15</td>
<td>1.50</td>
<td>0.56</td>
</tr>
<tr>
<td>Cocaine</td>
<td>30</td>
<td>80</td>
<td>2.67</td>
<td>1.00</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>24</td>
<td>85</td>
<td>3.54</td>
<td>1.33</td>
</tr>
</tbody>
</table>

Non-flu BZ, benzodiazepines other than flunitrazepam; GHB, gamma hydroxybutyrate.

### Table 2. Composite values for CNS depressants, stimulants and illicit drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>First phase</th>
<th>Second phase</th>
<th>Growth factor</th>
<th>Index of change</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS depressants</td>
<td>209</td>
<td>572</td>
<td>2.74</td>
<td>1.03</td>
</tr>
<tr>
<td>Stimulants</td>
<td>54</td>
<td>165</td>
<td>3.06</td>
<td>1.15</td>
</tr>
<tr>
<td>Illicit drugs</td>
<td>149</td>
<td>438</td>
<td>2.94</td>
<td>1.11</td>
</tr>
</tbody>
</table>

(CNS depressants: benzodiazepines, including flunitrazepam; barbiturates, ethanol, GHB. Stimulants: cocaine, amphetamine. Illicit drugs: GHB, cannabinoids, opiates, cocaine, amphetamine)

### Table 3. Summary of the sample set.

<table>
<thead>
<tr>
<th>Category</th>
<th>First phase</th>
<th>Second phase</th>
<th>Growth factor</th>
<th>Index of change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total samples</td>
<td>388</td>
<td>1033</td>
<td>2.66</td>
<td>1.00</td>
</tr>
<tr>
<td>Negative samples</td>
<td>138</td>
<td>422</td>
<td>3.06</td>
<td>1.15</td>
</tr>
<tr>
<td>Positive samples</td>
<td>250</td>
<td>611</td>
<td>2.44</td>
<td>0.92</td>
</tr>
<tr>
<td>Positive tests</td>
<td>338</td>
<td>980</td>
<td>2.90</td>
<td>1.09</td>
</tr>
</tbody>
</table>
this growth factor was divided by the increase in the total number of positive tests, it yielded an index of change in the number of detections for each of the individual drugs. Index of change values > 1 indicate an increasing frequency of positive tests over time, those < 1 indicate a decreasing frequency and those ≈ 1 indicate no change in time.

About 41 per cent of the specimens were negative (i.e. no drugs were detected). In the positive samples (at least one drug found), nearly 20 different substances were detected, with alcohol being the most common (37 per cent of all samples tested) followed by cannabinoids (18.5 per cent). During the first period (i.e. from June 1996–July 1997), four samples of 138 tested (1.2 per cent) were positive for flunitrazepam. Two further samples were positive for flunitrazepam during the second phase (August 1997–May 1998). The cumulative total for flunitrazepam was six of the 1033 samples tested (0.6 per cent). Of these, four samples contained other drugs, including alcohol, cocaine and/or morphine. Thus, in only 0.2 per cent of samples was flunitrazepam detected alone — it may be the case that alcohol was missed in these cases due to delay between ingestion and sampling.

As Table 1 indicates, the index of change (0.56) was lowest for flunitrazepam, GHB and codeine in comparison to the other drugs, implying a decreasing incidence of positive detections. The group of non-flunitrazepam benzodiazepines has the second lowest index value (0.82). In contrast, the index values for ethanol (1.27), cannabinoids (1.46), barbiturates (1.25) and amphetamines (1.33) indicate an increasing frequency of positive samples over time.
Interestingly, as Table 2 shows, the composite figures and respective indices for CNS depressants (1.03), stimulants (1.15) and illicit drugs (1.11) tend to equalize the sub-trends of individual substances, indicating a relatively unchanging frequency of detection in these composite groups.

The proportionate representation of the different drugs in all of the samples is illustrated by Figure 1. Overall, the most commonly detected drug was alcohol, which was present in 113 (29 per cent) of samples at the beginning of the monitoring period and in 382 (37 per cent) at the end. Figure 2 illustrates the cumulative totals of negative samples, and positive samples by drug, over the second phase of the study.

DISCUSSION

The overall incidence of flunitrazepam in samples taken from rape victims where substances were suspected was very low (0.6 per cent) compared to other benzodiazepines (12.5 per cent) and alcohol (37 per cent). Only 0.2 per cent of samples contained flunitrazepam alone — the others contained cocaine, alcohol and/or morphine. Due to the interval between ingestion and sampling, alcohol may have been missed in the flunitrazepam-alone samples. Furthermore, the index of change in incidence showed a trend towards a decreasing frequency of samples that were positive for flunitrazepam.

The majority (86.1 per cent) of samples were taken within 48 h of the alleged drug ingestion, and 97.5 per cent of the urine samples were taken within the sensitivity range of 72 h for flunitrazepam (Figure 3). Given the very low incidence rate of samples positive for flunitrazepam, it is unlikely that further positive samples would have escaped detection due to late urine sampling in the remaining 26 cases.

The relatively large number of negative samples (41 per cent) cannot be easily explained. Given the data on the time intervals from alleged drug ingestion to urine sampling and the time limits for detection, it is unlikely that benzodiazepines (including flunitrazepam), opioids or cannabinoids have been missed. In fact, a somewhat disproportionate over-representation of these drugs might be expected due to their plasma elimination half-lives. Conversely, it is likely that alcohol, amphetamines and cocaine are
under-represented for the same reason. The temporal and causal relationship between the substances detected and the alleged assaults is unknown for reasons of confidentiality.

The results indicate a considerable degree of multiple drug use, particularly alcohol combined with various other drugs, which may not be surprising in the context of what is already published about 'date' or 'acquaintance rape'. The test results also indicate a rather high incidence of illicit drugs, which may be related to the finding that female drug abusers are at a higher risk of being assaulted (Kilpatrick et al., 1997). Illicit drugs and alcohol are known to be significant risk factors for rape (Abbey, 1991; Hammock and Richardson, 1997; Harrington and Leitenberg, 1994; Koss and Dinero, 1989; Muehlenhard and Linton, 1987; Stormo et al., 1997).

Despite media reports, these results do not support the labelling of flunitrazepam as a 'date rape drug'. The incidence of samples positive for flunitrazepam was very low, and the trend for detection, if any, decreased over time. Survey research among typical patient populations with sleep and anxiety disorders suggests that flunitrazepam is characteristic of benzodiazepines in that it is used appropriately and conservatively, with low liability for abuse (Woods and Winger, 1997). Currently, over one million patients in 80 countries take flunitrazepam for insomnia and related disorders. For these legitimate users of the drug, flunitrazepam remains a valuable, safe and effective hypnotic.

REFERENCES


