

resistance phenomena in heavy drug-users should not be confused with tolerance which, if it is part of drug resistance, is usually considered to occur via specific receptor **desensitisation**. Most of the symptoms reported as abstinence phenomena (agitation, tachycardia, tachypnoea, restlessness, tremor, anxiety) may well be part of these two patients' psychiatric conditions. Misuse of zolpidem, which is not anxiolytic, to counteract a high anxiety level may have had an aggravating effect. The reported dose-escalation may have been linked to incorrect use as a sedative. The clinical relevance of these two cases for the correct use of zolpidem in insomniac patients is questionable.

The case described by Iruela and colleagues (August 14, p 443) can be considered as a typical example of hypnagogic visual illusions and/or hallucinations (DSM-III-R) occurring in a dream state.¹ However, the diagnosis of psychotic reaction is somewhat incorrect. We are confronted with a case of severe restrictive anorexia with probably a "heavy" internal subconscious experience (guilt feelings, sexual fears, polarised ideation). As specified in zolpidem's labelling, the drug has a rapid onset of action and should always be taken with the patient in bed with the lights turned off immediately. In Iruela and colleagues' patient, rapid absorption of zolpidem may have lowered vigilance, the patient became dreamy with hypnagogic distortion, and subjective intensification of the visual perception was accompanied by the re-emergence of fears and terrifying thoughts probably linked to the patient's internal experience. Some of the symptoms described are part of the patient's psychiatric condition (sexual fears, distorted body images). The kaleidoscopic character of the images also suggests an hypnagogic experience.

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1 Ey H. *Manuel de psychiatrie*. Masson SA, Paris, 1963.

Paracetamol and acute biliary pain with cholestasis

SIR—The hepatotoxic effects of paracetamol in acute overdose are well-recognised. Otherwise, this compound is generally regarded as **safe**.¹ We report acute biliary pain with cholestasis as a further complication of this drug.

A previously well 25-year-old teetotal Asian housewife was admitted with 2 days history of nausea and upper abdominal pain. She had right upper quadrant abdominal tenderness. Haematological and biochemical tests were normal. 3 days later her abdominal pain worsened. She was jaundiced and passed dark urine. Liver function tests became abnormal and reached their peak 10 days later, with bilirubin 160 $\mu\text{mol/L}$ (normal 3–15), **alanine** transaminases 287 IU/L (O-35), and alkaline phosphatase 440 IU/L (70-300). She admitted to having taken about 12 paracetamol tablets per day for 3 or 4 days for toothache before the onset of her current symptoms. Throughout, clotting profile was normal. Repeated ultrasound scan of her abdomen showed a normal gall bladder, biliary tree, and liver. Full liver screen² for other causes was negative. Endoscopic retrograde cholangiopancreatogram and dynamic computed tomography with contrast were also normal. A liver biopsy was done because of continuing abnormal liver function tests, and this revealed bile plugging in the canaliculi, indicative of cholestasis. Eventually, her liver function returned to normal 5 months after the onset and she has remained symptom-free at 2 years.

Acute, paracetamol-induced liver injury usually involves dramatic increases in plasma aminotransferases with moderate

rises in plasma bilirubin and prothrombin time **ratios**.² Clinically, patients may have only nausea and vomiting, and severe cases may develop fulminant hepatic failure and die. Our patient had a different clinical picture, suggesting that depletion of hepatic glutathione and the generation of the toxic metabolite N-acetylbenzoquinonimine that is found in cases of acute overdose was probably not responsible for her symptoms. Paracetamol ingested at therapeutic dose can cause a picture resembling chronic active **hepatitis**,³ possibly resulting from a low-grade drug-induced hepatic injury. Waldum et al⁴ reported cases of periodic acute cholestasis in two women that developed some time after the ingestion of either aspirin, paracetamol, or naproxen. In both cases, ingestion of one or other of these drugs at standard doses led within 24-48 hours to admission with acute abdominal pain and deranged liver function.

Paracetamol is a weak inhibitor of **cyclo-oxygenase**,⁵ and prostaglandins may regulate the contraction of the sphincter of **Oddi**. Susceptible individuals may develop acute cholestasis because of hypersensitivity to prostaglandins, induced by drugs that inhibit **cyclo-oxygenase**.⁴ Conversely, the ability of prostaglandins to reduce bile flow and bile secretion would imply that cyclo-oxygenase inhibitors could increase fluid pressure in the bile duct, possibly leading to cholestasis if taken for long enough at sufficient doses. The complication we describe occurred in a patient without pre-existing hepatic dysfunction, when paracetamol was taken in excess of the recommended dose, and the drug does not necessarily produce long-standing liver **damage**.²

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- 1 Pessayre D, Larrey D. **Drug-induced liver injury**. In: McIntyre N, Benhamou J-P, Bircher J, Rizzetto M, Rodes J, eds. *Oxford University Press*, 1991: 875-902.
- 2 Prescott LF. **Liver damage with non-narcotic analgesics**. *Med Toxicol* 1986; 1: 44-56.
- 3 Johnson GK, Tolman KG. **Chronic liver disease and acetaminophen**. *Ann Intern Med* 1977; 87: 302-04.
- 4 Waldum HL, Hamre T, Kleveland PM, et al. **Can NSAIDs cause acute biliary pain with cholestasis?** *J Clin Gastroenterol* 1992; 14: 328-30.
- 5 Humes JL, Winter CA, Sadowski S J, Kuehl FA. **Multiple sites on prostaglandin cyclooxygenase are determinants in the action of non-steroidal anti-inflammatory agents**. *Proc Natl Acad Sci USA* 1981; 78: 2053-56.

Non-surgical female sterilisation

SIR—Hieu and colleagues' report (July 24, p 213) about quinacrine pellets for non-surgical sterilisation in women provides encouraging evidence that we may be close to a much-needed, safer, more acceptable alternative to conventional sterilisation. Nevertheless, one of their assertions that operator skill "dominated the determinants of efficacy" is not supported by their data. Indeed, the evidence that they provide on the amount of operator experience contradicts this assertion.

Hieu and co-workers divide operators into two groups (table 3)—those who had one or more failures, and those who had none. Each of these groups was, in turn, divided by the number of procedures performed. For operators who had at least one failure, the mean failure rate was 5.9 per 100 procedures. Hieu states without providing a test statistic, that "the failure rate was the highest among operators who had done 10 or fewer insertions (17.2%) and lowest among those who had done more than 100 (5.3%)".

The appearance of a high failure rate in the group with 10 or fewer insertions is an artifact of two imposed conditions: (1)

having at least one failure; and (2) the classification restricting the number of procedures for each member of the group to 10 or fewer. Irrespective of the skills of the operators in this group, by having at least one failure, the failure rate had to be 10% (or more), which is well above the mean. An analogy would be examination of the success of individuals playing the slot machines who both deposited 10 or fewer coins and won a jackpot. The return on investment would be spectacular for those fortunate few individuals, even though overall the first 10 chances of success are no different from any other.

In my view, the meaningful analysis of failure related to experience is the last third of table 3, which does not segregate by whether the operator had at least one failure, and indicates no apparent difference by number of procedures per operator. An alternative analysis might be to look at failure rates of individual operators over time to see if progressively greater experience reduces failure, but these data are not presented. Hieu and colleagues may have some other indication of operation skill besides experience, but these are not reported. Nevertheless, it may well be an advantage of this simple method if success is not dependent on operator experience.

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SIR—One should reserve judgment about efficacy and perhaps safety of quinacrine pellets for non-surgical sterilisation as reported by Hieu and colleagues, because studies included in their life-table analysis (table 2) yield lower pregnancy rates than do the data omitted from the table.

Life-table rates allow inclusion of all durations of follow-up—ie, the scheduled 1, 3, and 6 month and half yearly visits—and of events occurring between follow-up visits. Table 2 shows that hundreds of women with fewer than 6 months of follow-up were included in the life-table analysis. They were in studies labelled **Haihung 2**, **Talbinh**, **Nghean 1**, and **Haihung 3**. These were studies of at least 50 cases followed for 12 months. The 11 686 cases in the life-table represent 36·8% of all quinacrine sterilisations. By calculation, women represented in the life-table had a total of 412 (SD 5) pregnancies in 14 948 (59) woman-years, an overall rate of 2·76 pregnancies per 100 woman-years. The first 6-month failure rate for these subjects was 4·28 per 100 woman-years. For the two-insertion procedure the first 6-month failure rate was 3·13 per 100 woman-years, about double the 6-month life-table cumulative rate for the procedure (because the life-table rate is for half a year).

For all cases, the ectopic pregnancy rate was 0·89 per 1000 woman-years on the basis of 19 ectopic pregnancies. This finding indicates that the total recorded exposure was 20 348 woman-years. There were 8 18 pregnancies (table 1). Therefore the 20 095 women not in the life-table had 406 (5) (= 8 18-4 12 [5]) pregnancies in 6400 (59) (= 21 348-14 948 [59]) woman-years. Their pregnancy rate, 6·34 per 100 woman-years, is more than double the 6-month failure rate of 3·13 per 100 woman-years for the two-insertion method ($p < 0\cdot001$), suggesting some selection of the studies included in the life-tables (table 2). It is difficult to understand the exclusion of Hatinh province from the life-table analyses, since 25 livebirths were recorded subsequent to the quinacrine procedure, and one guesses that at least 50 women had one year's experience after the procedure. In Hatinh province there were 91 pregnancies after 997 procedures.

The life-table analyses should have included all women with follow-up. Table 1, which presented data on all cases, should have shown separate data for the one-insertion and two-insertion procedures to allow their evaluation.

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SIR—The method of non-surgical female sterilisation investigated by Hieu and co-workers has great potential in Vietnam, and the prospect of a full-time family-planning worker at every commune health station, mentioned by Feuerstein in her accompanying commentary (p 188), is encouraging. However, enthusiasm for female sterilisation should be carefully tempered.

The principle of individual choice in family planning means that services must not be prescriptive and that professionals should avoid being patronising about the suitability of specific methods. No drugs, device, or procedure is without side-effects: the decision about which family-planning method to use has to rest with the individual, who should be properly informed about the risks and benefits. Sterilisation may provide an expedient way of achieving official targets but coercion should be avoided.

As in most developing countries, the government budget allocated to family planning in Vietnam is inadequate. Now that investigations demonstrating the safety of injectable contraceptives^{1,2} have allayed previous concerns³ it is to be hoped that research on injectable contraceptives in Vietnam will soon lead to improved health-service delivery. International development agencies should promote the inclusion of injectable contraceptives in the "cafeteria model" aimed at providing a wide range of choice. That may mean advocacy on the agencies' part so that injectable contraceptives are licensed in western donor countries. We must avoid the perception that injectable contraceptives have side-effects that make them inappropriate for donor countries but suitable for dumping in the third world.⁴ The unique advantages of injectable contraceptives must be emphasised.⁵

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Authors' reply

SIR—Shelton assumes that skill and experience are related, and his comments are based on this premise. We believe that with this method, evidence shows that skill and experience are not related. We defined skill as the "consistent application of proper insertion technique". The application of improper technique or the inconsistent application of proper technique would be poor skill, no matter how much experience an operator had of a method. This large field trial offers a unique opportunity to study differences in failure rates of a large number of clinicians (over 1300). We agree that the most meaningful analysis of failure related to experience is the last third of table 3. We believe that it provides compelling evidence that increasing experience does not improve the skill of the operator. If it did so then the overall failure rate would fall as the size of individual series increased. It did not.

More importantly, we agree with Shelton that a better alternative analysis would be to look at failure rates of individual operators over time to see if progressively greater experience reduces failure. This analysis was initially undertaken and we found that failures were distributed throughout individual clinicians' series (much to our surprise) and not concentrated early in each series as one would expect if