1 McCann UD, Tuan J, Hatzidimitriou G, Ricaurte GA. Selective serotonin reuptake inhibitors dissociate fenfluramine's anorectic and neurotoxic effects: Importance of dose, species and drug. *J Pharmacol Exp Ther* 1997; **281:** 1487–98.
2 Ricaurte GA, DeLanney LE, Irwin I, et al. Toxic effects of 3,4-mathylenedioxy-methamphetamine on central serotonergic neurons in the primate: Importance of route and frequency of drug administration. *Brain Res* 1988; **446:** 165–68.
3 McCann U, Mertl M, Ricaurte G. Methylenemethamphetamine (MDMA, "Ecstasy"). In: Tarter R, Ammerman R, Ott P, eds. In: Handbook of substance abuse: neurobehavioural pharmacology. New York, Plenum Press, 1998: 567–78.

Fatal MDMA intoxication

Sir—J A Henry and I R Hill (Nov 28, p 1751)[1] report a fatal interaction between ritonavir and 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). MDMA plasma concentrations measured in their patient largely exceeded those expected after ingestion of 180 mg MDMA. They argue that concomitant treatment with ritonavir could be responsible for a metabolic interaction between both drugs, leading to toxic concentrations of MDMA, and that CYP2D6 (a polymorphic isoenzyme of cytochrome P450) would be involved in such interaction.[2] Ritonavir is mainly a CYP3A substrate and secondarily a CYP2D6 and CYP2C9 substrate. Clinical interactions reported until now with CYP2D6 substrates seem less relevant than those associated with CYP3A.[3]

As the investigators mention, three factors should be taken into account: the patient had an impaired liver function because of alcoholism; treatment with ritonavir was started 2 weeks before the accident; and his status as an extensive or poor metaboliser for CYP2D6 substrates was unknown. All three factors would have determined a metabolic impairment of drugs clearance. On the other hand, the patient gave a history of having taken two tablets of ecstasy (about 140 mg) with little effect, and as soon as a further half tablet was ingested, he experienced the initial symptoms of MDMA intoxication.

We would like to propose a non-linear pharmacokinetics of MDMA as another explanation for this case of fatal MDMA intoxication. In the context of a series of clinical studies in 14 healthy volunteers with experience in the recreational use of MDMA, in which different doses of MDMA were tested to select the most adequate for further pharmacological studies of the drug,[4] an unexpected phenomenon was observed. The following doses were tested: 50 mg (n=2), 75 mg (n=8), 100 mg (n=2), 125 mg (n=8), and 150 mg (n=2). MDMA plasma and urinary concentrations were measured in all the participants.[5] All participants were phenotyped as extensive metabolisers by means of dextromethorphan as a probe drug for CYP2D6 activity. A preliminary analysis of MDMA area under the plasma concentration versus time curve (AUC_{0-24h}) and peak plasma concentrations (C_{max}) suggested a non-linearity in the pharmacokinetics of MDMA. Although there was a factor of 3 in the range of doses given (50–150 mg), AUC_{0-24h} and C_{max} increased by a factor of 10 and 6, respectively:

MDMA dose (mg)	AUC $_{0-24\,h}$ (ng mL^{-1} h^{1})	C $_{max}$ (ng/mL)
50	457 (505)	51 (45)
75	1332 (646)	126 (38)
100	2057 (283)	190 (20)
125	2624 (573)	229 (46)
150	5439 (411)	465 (122)

Data are mean (SD).

The lack of linearity of MDMA pharmacokinetics implies that fairly small increases in the dose of MDMA ingested could lead to disproportionate increases in MDMA plasma concentrations and, consequently, with an increased risk for MDMA acute intoxication. In addition to drug to drug interactions and the individual's metabolic status, which Henry and Hill mention, a possible phenomenon of non-linear pharmacokinetics could be another factor that may explain the high plasma concentrations of MDMA.

This study was supported by grants FIS 97/1198, CIRIT (1997SGR00077), ISCIII 97/4344 and Plan Nacional sobre Drogas, Madrid

*Rafael de la Torre, Jordi Ortuño, Marta Mas, *Magi Farré, Jordi Segura*
Unit of Pharmacology, Institut Municipal d'Investigació Mèdica, E-08003, Barcelona, Spain
(e-mail: mfarre@imin.es)

1 Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. *Lancet* 1998; **352:** 1751–52.
2 Tucker GT, Lennard MS, Ellis SW, et al. The demethylenation of methylenedioxyamphetamine ("ecstasy") by debrisoquine hydroxylase (CYP2D6). *Biochem Pharmacol* 1994; **47:** 1151–56.
3 Hsu A, Granneman R, Bertz RJ. Ritonavir. Clinical pharmacokinetics and interactions with other anti-HIV agents. *Clin Pharmacokinet* 1998; **35:** 275–91.
4 Cami J, de la Torre R, Ortuño J, et al. Pharmacokinetics of ecstasy (MDMA) in healthy subjects. *Eur J Clin Pharmacol* 1997; **52** (suppl): A168.
5 Ortuño J, Pizarro N, Farré M, et al. Quantification of 3,4-methylenedioxymethamphetamine (MDMA) and its metabolites in plasma and urine by gas chromatography with nitrogen-phosphorous detection (GC/NPD). *J Chromatogr B* (in press).

Sir—Entactogens represents a class of psychoactive synthetic compounds abused as recreational designer drugs, for example MDMA, methylene-dioxyethylamphetamine (MDE), or 3,4-methylenedioxyamphetamine (MDA). Originally these drugs were regarded as being "safe", but an increasing number of severe adverse effects and even deaths have been reported, such as the report by J A Henry and I R Hill.[1] Additionally, several cases of MDMA-induced hepatic damage requiring subsequent liver transplantation have been described.[2,3]

The responsible underlying mechanism is still unclear. One possible explanation is that deficiency in cytochrome P4502D6 (CYP2D6) expression could be a genetic factor that predisposes to an increased risk of MDMA-related toxic effects due to an accumulation of MDMA or MDMA-related drugs. In-vitro studies have shown that demethylenation of MDMA, MDA, and MDE is a major metabolic pathway catalysed by the CYP2D6 enzyme.[4] This enzyme exhibits a genetic polymorphism with 7–10% of white people expressing no functional enzyme (poor metaboliser).[5]

To assess this question for the first time three patients admitted for MDMA-related hepatotoxicity were genotyped for CYP2D6 alleles, which allows a correct prediction of the poor metabolisers phenotyped in more than 99% of white people.[5] Two of these patients, whose case histories were published in 1997, had MDMA-induced fulminant hepatic failure and subsequent liver transplantation. Both patients had regularly taken MDMA on weekends for several months without any side-effects. After a further intake of MDMA, they developed fulminant hepatic failure: the histopathology revealed massive liver necrosis.[2,3] Screening for hepatic viruses was negative.

The third patient, a 17-year-old woman had recurrent periods of massive right-upper quadrant abdominal pain and jaundice. The laboratory findings revealed only raised concentrations of liver enzymes; serological tests for hepatitis A, B, and C virus, cytomegalovirus, Epstein-Barr virus, and antinuclear, antimito-chondrial and smooth-muscle antibodies were negative. Other causes of jaundice could be ruled out. A liver biopsy specimen showed toxic hepatitis characterised by lobular disarray with swollen hepatocytes, centrolobular necrosis with activated Kupffer cells, and a large amount of ceroid pigment surrounded by infiltrates of inflammatory cells,

predominantly lymphocytes and eosinophils. Although the patient denied drug abuse, MDA (0·92 ng per mg hair) and low concentrations of amphetamines (1·27 ng/mg hair) were detected in hair analysis.

12 CYP2D6 alleles (five functional alleles: CYP2D6*1,*2,*2xN, *9, *10; seven non-functional alleles: CYP2D6*3, *4, *5, *6, *7, *8, *16) were analysed by allele-specific PCR directed against one or more relevant mutated sites.

The three patients were identified to be extensive metabolisers (not poor metabolisers), since they were not carriers of two non-functional CYP2D6 alleles. The genotypes for the three patients were *1/*4, *2/*5, *1/*1. Thus, the hypothesis that higher plasma concentrations of MDMA or MDMA-related drugs, resulting from genetically impaired metabolism, are responsible for hepatotoxicity seems unlikely.

Nevertheless, the causal role of MDMA in hepatotoxicity is evident. The histopathological pattern of liver damage is almost identical in the described cases, including our patients, and the hepatotoxicity cannot be exclusively explained by a potentially toxic contaminant in MDMA tablets. Examinations of seized MDMA tablets have shown varying contents of MDMA, MDA, MDE, amphetamines, and additives such as disaccharide, without pharmacological potency. Hyperthermia itself as another cause of liver damage could be excluded because hyperpyrexia was not observed in the three described cases.

Thus, inherited CYP2D6 deficiency seems to be unrelated to MDMA-induced hepatotoxicity. We suggest an idiosyncratic type of reaction because the severity of liver damage correlates neither with the amount nor with the frequency of MDMA ingestion.

Matthias Schwab, Eva Seyringer, Robert B Brauer, Achim Hellinger, Ernst-Ulrich Griese

For full authorship see www.thelancet.com

*Dr Margarete Fisher-Bosch Institute of Clinical Pharmacology, 70376 Stuttgart, Germany; Department of Gastroenterology, General Hospital, Wels, Austria; Department of Surgery, Klinikum Rechts der Isar, Technical University Munich, Munich; and Department of Surgery, University Marburg, Marburg

1 Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. *Lancet* 1998; **352:** 1751–52.

2 Brauer RB, Heidecke CD, Nathrath W, et al. Liver transplantation for the treatment of fulminant hepatic failure induced by the ingestion of ecstasy. *Transpl Int* 1997; **10:** 229–33.

3 Hellinger A, Rauen U, de Groot H, et al. Auxiliary liver transplantation for acute liver failure after long-term intake of ecstasy tablets (3,4 methylenedioxymethamphetamine). *Deut Med Wochenschr* 1997; **122:** 716–20.

4 Tucker GT, Lennard MS, Ellis SW, et al. The demethylenation of methylenedioxy-methamphetamine (ecstasy) by debrisoquine hydroxylase (CYP2D6). *Biochem Pharmacol* 1994; **7:** 1151–56.

5 Griese E-U, Zanger UM, Brudermanns U, et al. Assessment of the predictive power of genotypes for the in-vivo catalytic function of CYP2D6 in a German population. *Pharmacogenetics* 1998; **8:** 15–26.

Epidural analgesia and risk of caesarean section

Sir—Marilyn Larkin's Jan 2 news piece[1] gives a disappointing review of a report by Halpern and colleagues[2] that reports no association between epidural analgesia and risk of caesarean section. It is doubtful *The Lancet* would have accepted the paper by Halpern, judging from Richard Horton's Jan 16 commentary.[3]

The heterogeneity among the trials selected by Halpern means adding up apples, oranges, and seven other types of fruit. There is substantial variability among all trials in terms of groups, dose, route and timing of drug, and use of oxytocin. Some trials use intention to treat analysis, whereas others do not—the investigators admit this variation produces significant demographic differences between trials. Over half the trials had significant crossover rates. As a result of these methodological weakness, it can not be said, as Larkin does, that the link between epidural analgesia and risk of caesarean section is disproved.

Halpern's unbalanced presentation is too much like a sales pitch for the use of epidural analgesia during labour. For example, Halpern and colleagues urge warning women of the dangers of parenteral opioid labour analgesia, but fail to urge warning women of the dangers of epidural labour analgesia, which they earlier list as including lengthy first and second stages of labour, increased use of oxytocin, instrumental vaginal delivery, maternal fever, and maternal hypotension.

Missing from all the trials reported are studies that compare epidural analgesia during labour with non-pharmacological methods of pain relief during labour. Drug research begins with trials that compare drug use with no drug use. Until such studies are done, we have no baseline data on risks of epidural analgesia during labour.

Marsden Wagner

2950 Van Ness St NW, Apartment 911, Washington DC 20008, USA
(e-mail: marsden.patricia@erols.com)

1 Larkin M. Link between epidural analgesia and risk of caesarean section disproved. *Lancet* 1999; **353:** 45.

2 Halpern S, Leighton B, Ohlsson A, Barnett J, Rice A. Effect of epidural vs parenteral opioid analgesia on the progress of labor. *JAMA* 1998; **280:** 2105–10.

3 Horton R. The information wars. *Lancet* 1999; **353:** 164–65.

Kidney cancer

Sir—In their seminar, Nicholas Vogelzang and Walter Stadler (Nov 21, p 1691)[1] state that, in the management of kidney cancer, "radiotherapy is never used as a primary treatment but is likely to be ineffective because of the radiation resistance of most metastatic lesions". They are half right.

Radiotherapy is almost never used for treatment of the primary cancer or as a routine adjuvant to nephrectomy. Radiotherapy is, on the other hand, frequently used to good effect in the palliative management of metastatic kidney cancer.

Clinical series document the efficacy of 2–4 weeks of radiotherapy for bone and soft-tissue metastases of kidney cancer. DiBiase and colleagues[2] treated 107 patients to 150 sites of metastatic disease and reported overall response rates of 99% in bone, 94% in soft tissue, and 100% in lung. Huguenin and colleagues[3] reported pain palliation in 56% of 34 sites, Halperin and Harisiadis[4] described a reduction in pain at 77% of 36 sites and Seitz and co-workers[5] noted subjective improvement in pain and improvement in clinical condition in 54% of 39 patients. The response rate of brain and spinal cord metastases has a broader range and seems to be lower (30–90%), but may be improved by stereotactic radiosurgery.[2,4]

The efficacy of palliative radiotherapy in kidney cancer is similar to that of other solid adult tumours and is a valuable tool in the management of advanced malignant disease.

Edward C Halperin

Department of Radiation Oncology, Duke University Medical Center, NC 27710, USA

1 Vogelzang NJ, Stadler W. Kidney cancer. *Lancet* 1998; **352:** 1691–96.

2 DiBiase SJ, Valicenti RK, Schultz D, Xie Y, Gomella LG, Corn BW. Palliative irradiation for focally symptomatic metastatic renal cell carcinoma: support for dose escalation based on a biological model. *J Urol* 1997; **158:** 746–49.

3 Huguenin PU, Kieser S, Glanzmann C, Capaul R, Lutolf UM. Radiotherapy for metastatic carcinomas of the kidney or melanoma: an analysis using palliative end points. *Int J Rad Oncol Biol Phys* 1998; **41:** 401–05.

4 Halperin EC, Harisiadis L. The role of radiation therapy in the management of metastatic renal cell carcinoma. *Cancer* 1983; **51:** 614–17.

5 Seitz W, Karcher KH, Binder W. Radiotherapy of metastic renal cell carcinoma. *Sem Surg Oncol* 1998; **4:** 100–02