Psychopharmacology (2009) 204:375–378
DOI 10.1007/s00213-008-1453-8

COMMENTARY

MDMA: On the translation from rodent to human dosing

A. Richard Green · Johan Gabrielsson · Charles A. Marsden · Kevin C. F. Fone

Received: 20 October 2008 / Accepted: 21 December 2008 / Published online: 13 January 2009

The recent paper in this journal by Goni-Allo et al. (2008) was a welcome addition to the literature on the effects of MDMA in rodents because it examined functional changes and related them to the systemic exposure (e.g., plasma concentrations) of the drug. Such pharmacodynamic–pharmacokinetic (or quantitative pharmacology) studies are vital if we are to attempt to relate preclinical findings to the possible acute and long-term consequences of human ingestion of MDMA. The debate on whether preclinical findings on the serotonergic neurotoxicity induced by MDMA in the rodent brain can be extrapolated to human recreational usage has engaged scientists' minds for around 20 years. Concerns have been raised as to whether the administered dose of MDMA typically used to cause neurotoxicity in rats allows any translational projections to be made as to the doses required to produce similar damage in the brains of humans following recreational use of the drug. These concerns are discussed in this short article.

In order to extrapolate doses used in animal studies to those in man it has been suggested by some (McCann and Ricaurte 2001) that the technique of interspecies scaling (Mordenti and Chappell 1989) should be used. Based on similar exposure (AUC, Css) to MDMA in rats and humans, this proposes that using the equation $D_{\text{human}}=D_{\text{animal}}(W_{\text{human}}/W_{\text{animal}})^{0.7}$ (where D is dose in milligram and W is weight in kilogram) allows calculation of equivalent doses in animals and humans. Accordingly, the dose of 20 mg/kg in rats becomes equivalent to a human dose of 280 mg (4 mg/kg) or somewhat over three ecstasy tablets. Other investigators (Sessa and Nutt 2008) have intimated that a dose of (for example) 20 mg/kg given by intraperitoneal injection to rats can be directly extrapolated and therefore proposed that a similar oral dose is required by human users to achieve a similar effect. So, a 20 mg/kg dose in rats is deemed "equivalent" to a 1,400 mg dose (20 mg/kg × 70 kg body weight) which is around 20 ecstasy tablets.

Of course, neither of these approaches has been shown to be valid for MDMA. Furthermore, the common practice of relating the pharmacological response directly to the administered dose is basically flawed. In examining the pharmacodynamics of a specific compound, factors like bioavailability, active metabolites, plasma protein binding differences, and pattern of systemic exposure can all play a major role in determining the onset, intensity, and duration of final effect. Since the exposure patterns of MDMA and active metabolite(s) can vary markedly between species, they confound any simple interpretation on a drug effect at any specific dose in one species producing a quantitatively similar effect in another, since it is impossible for all of the administered substance (at any stated dose) to be responsible for the observed pharmacological effect. For intelligent interpretation of any data collected, it is important at the very least to have a measurement of "exposure" of parent and potentially active metabolites and by that we mean the AUC or average concentration within a dosing interval or the peak plasma concentration that occurs following drug administration. Ideally, this means the unbound plasma concentration. This still fails to take into account the half-life of the drug, plasma protein binding (which can even change with plasma drug concentration in the same species), and the pharmacological action of active

A. R. Green (✉) · C. A. Marsden · K. C. F. Fone
Institute of Neuroscience, School of Biomedical Sciences,
Queen's Medical Center, University of Nottingham,
Nottingham NG7 2UH, UK
e-mail: richard.green@nottingham.ac.uk

J. Gabrielsson
Discovery DMPK and BAC, AstraZeneca R and D Mölndal,
S-431 83 Mölndal, Sweden

metabolites, such as 3,4-methylenedioxyamphetamine in the case of MDMA. In humans at least, there is mechanism-based inhibition of MDMA metabolism (de la Torre et al. 2000; Mathúna et al. 2008). In practice, this means that the more circulating MDMA available (the higher systemic exposure), the more the toxic pathway is inhibited. Furthermore, most rodent studies utilize intraperitoneal or subcutaneous MDMA administration, rather than oral administration as occurs in humans, further complicating the pharmacokinetics by influencing bioavailability and/or metabolism. All these factors mean that even measuring exposure provides limited information. Nevertheless, it is a distinct advance on relying entirely on the dose administered to extrapolate from one species to another, and it provides valuable information to other scientists.

There are now available several good pharmacokinetic studies on MDMA in both rats and humans, and we have used these to make a simple examination of the relevance of rat dosing to human drug ingestion. Human dosing was always by oral administration, and five studies were included (de la Torre et al. 2000; Farré et al. 2007; Hernandez-Lopez et al. 2002; Kolbrich et al. 2008; Mas et al. 1999). When dosing has not given in milligram/kilogram, this was calculated by dividing the stated administered dose in mg by the mean weight of experimental subjects. The data on rats were taken from six studies (Chu et al. 1996; Goni-Allo et al. 2008; Hiramatsu et al. 1991; Morley-Fletcher et al. 2004; Upreti and Eddington 2007; Valtier et al. 2007). The rat studies used oral, intraperitoneal and subcutaneous routes of administration and three different strains (Wistar, Sprague–Dawley, and Dark Agouti). However, despite the varied routes of administration and various strains of rat used, the peak plasma concentration (taken as occurring within 1–3 h post-administration) at any one dose was similar across the studies, and it was, therefore, considered reasonable to use a mean value obtained from all studies that used the same administered dose.

The MDMA dose-plasma concentration response curves for humans and rats are shown in Fig. 1. The fact that there is auto-inhibition of MDMA metabolism in humans (de la Torre et al. 2000) is apparent in the increased gradient of the slope as the dose increases (Fig. 1, insert graph). A dose of 1 mg/kg gives a C_{max} of about 100 μg/l, whereas doubling the dose (2 mg/kg), increases C_{max} > fourfold to 450 μg/l. For both safety and ethical reasons, humans do not appear to have received greater than approximately 2 mg/kg.

In contrast, several studies in rats report doses of up to 20 mg/kg. The graph fails to reveal clear evidence for auto-inhibition of MDMA metabolism in the rat. However, what is most apparent is that a dose of 2 mg/kg in humans produces a peak plasma concentration that is only achieved

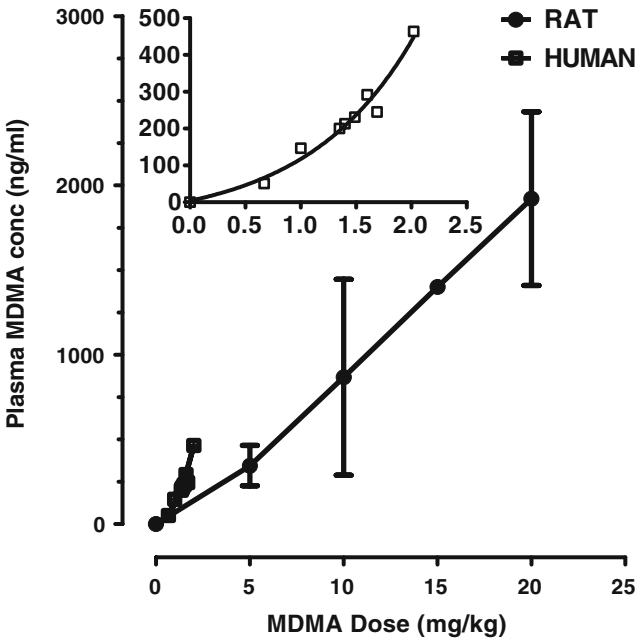

Fig. 1 Plot of mean values of peak plasma MDMA concentration versus dose of MDMA administered taken from publications examining these two parameters in studies on rats and humans (references given in main text). Data in rats shown as mean value ± SEM of values from each study at that dose; data in humans shows each separate study value obtained. Variance in these studies can be ascertained from the original papers. *Insert figure* shows human data in an expanded graph for clarity

by giving approximately 7 mg/kg to rats. Thus, a fourfold higher dose is required in rats to produce a similar peak blood plasma exposure to that seen in humans. Functional observations suggest that this is a reasonable interpretation given that a 100 mg MDMA dose (1.4 mg/kg) provokes a 0.6°C oral temperature rise in humans (Farré et al. 2007) and a similar increase in rectal temperature is seen following an approximate fourfold higher dose (5 mg/kg IP) to rats (Colado et al. 1995). Interestingly this rat–human dose ratio is similar to that produced by using the interspecies scaling calculation (see above). In contrast, the results presented here make clear that the "direct extrapolation of dose" technique is naive and with no credibility. While any projection of higher doses in humans to a specific plasma concentration is difficult, given the lack of data, extrapolation of the graph does suggest that even a small increase in dose would lead to a marked increase in plasma concentration. Since concentrations well in excess of 1,000 μg/l have been detected in patients admitted with acute MDMA-induced toxicity (Greene et al. 2003), this interpretation also appears to be valid.

The lack of known mechanism-based inhibition of MDMA metabolism in rat may be the primary problem in extrapolating from rat to human. Binge dosing (repeated small dosing as used by some recreational users with the aim of preventing the occurrence of acute adverse effects) is

likely to produce no more than additive effects in rats and an additive effect is indeed seen in the hyperthermic response (Green et al. 2004). In contrast, since the first dose of MDMA in humans inhibits metabolism within an hour (Yang et al. 2006), further dosing may induce a greater than additive temperature response. Consequently binge dosing experiments in rats may prove to be a poor model for the acute consequences in humans.

Measurement of the binding of MDMA to plasma proteins in rats and humans would assist further in reaching an accurate comparison of unbound MDMA and metabolite concentration(s) between species, since we may presume that only the unbound drug is available for transport into the brain and binding of a drug can vary markedly between species. However, no data, apart from values obtained in dogs (Garrett et al. 1991), are available.

It is also worth pointing out that measurement of drug exposure should generally be the norm in all experimental models used, but particularly in any that are subject to greater ethical concerns such as primate studies, in order to obtain the maximum useful information from the study. Had that been done the erroneous report on the toxic effect of MDMA on dopamine nerve endings in primate brain (Ricaurte et al. 2002) would not have been published as the investigators would have rapidly discovered that the animals had in fact been administered methamphetamine rather than MDMA because of an error by the organization supplying them with the drug (Ricaurte et al. 2003).

Recently Sessa and Nutt (2007) suggested that MDMA might be used as a psychotherapeutic agent. We concurred with them that the doses proposed would be unlikely to produce an acute adverse effect (Green et al. 2008). However, we also pointed out that the possibility of long-term neurotoxicity, as has been well established to occur in the rodent brain (Green et al. 2003), remained a valid concern. Sessa and Nutt cast doubt on our concerns by citing an "equivalence of dose" calculation which we have now shown to lack validity. However, when considering neurotoxicity, we suggest that further pharmacokinetic and drug metabolism studies become even more vital. MDMA does not itself produce neurotoxicity in the brain; rather, it results from peripherally formed metabolites (Esteban et al. 2001). Thus, the rate and extent of absorption and metabolism of MDMA may be vital, since slower metabolism may prevent the rapid accumulation of toxic metabolites and an overwhelming of detoxification mechanisms (Yang et al. 2006). Lack of knowledge as to the identity of the toxic metabolite or metabolites limits further useful discussion other than to point out that hepatic metabolism of MDMA in rats and human may differ (see Easton and Marsden 2006); it certainly differs in rat and mouse (see de la Torre and Farré 2004) which may, in part, account for serotonergic neurotoxicity not being a major consequence of MDMA administration to the mouse (O'Shea et al. 2001). Consequently extrapolation as to what is "safe" in humans based on data obtained in rats remains risky. These arguments are expanded further by de la Torre and colleagues elsewhere (de la Torre and Farré 2004; de la Torre et al. 2004).

In conclusion, this commentary is making a plea for future preclinical pharmacological research on MDMA to be linked much more closely to appropriate exposure analysis coupled to parent compound and potentially neurotoxic metabolite(s), in order that informed extrapolation may be made as to the likely acute and long-term effects of this popular recreational drug in human users.

References

Chu T, Kumagai Y, DiStefano EW, Cho AK (1996) Disposition of methylenedioxymethamphetamine and three metabolites in the brains of different rat strains and their possible roles in acute serotonin depletion. Biochem Pharmacol 51:789–796

Colado MI, Williams JL, Green AR (1995) The hyperthermic and neurotoxic effects of 'Ecstasy' (MDMA) and 3,4 methylenedioxyamphetamine (MDA) in the Dark Agouti (DA) rat, a model of the CYP2D6 poor metabolizer phenotype. Br J Pharmacol 115:1281–1289

de la Torre R, Farré M (2004) Neurotoxicity of MDMA (ecstasy): the limitations of scaling from animals to humans. Trends Pharmacol Sci 25:505–508

de la Torre R, Farré M, Ortuno J, Mas M, Brenneisen R, Roset PN, Segura J, Cami J (2000) Non-linear pharmacokinetics of MDMA ('ecstasy') in humans. Br J Clin Pharmacol 49:104–109

de la Torre R, Farré M, Roset PN, Pizarro N, Abanandes S, Segura M, Segura J, Cami J (2004) Human pharmacology of MDMA, pharmacokinetics, metabolism and disposition. Ther Drug Monit 26:137–144

Easton N, Marsden CA (2006) Ecstasy: are animal data consistent between species and can they translate to humans? J Psychopharmacol 20:194–210

Esteban E, O'Shea E, Camarero J, Sanchez V, Green AR, Colado MI (2001) 3,4-methylenedioxymethamphetamine induces monoamine release but not toxicity when administered centrally at a concentration occurring following a peripherally injected neurotoxic dose. Psychopharmacology 154:251–260

Farré M, Abanades S, Roset PN, Peiro AM, Torrens M, O'Mathuna B, Segura M, de la Torre R (2007) Pharmacological interaction between 3,4-methylenedioxymethamphetamine (ecstasy) and paroxetine: pharmacological effects and pharmacokinetics. J Pharmacol Exp Ther 323:954–962

Garrett ER, Seyda K, Marroum P (1991) High performance liquid chromatography assays of the illicit designer drug "ecstasy", a modified amphetamine, with applications to stability, partitioning and plasma protein binding. Acta Pharm Nord 3:9–14

Goni-Allo B, Mathúna BÓ, Segura M, Puerta E, Lasheras B, de la Torre R, Aguirre N (2008) The relationship between core body temperature and 3,4-methylenedioxymethamphetamine metabolism in rats: implications for neurotoxicity. Psychopharmacology 197:263–278

Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI (2003) The pharmacology and clinical pharmacology of 3, 4-methylenediox-

ymethamphetamine (MDMA, "ecstasy"). Pharmacol Revs 55:463–508

Green AR, Sanchez V, O'Shea E, Saadat KS, Elliott JM, Colado MI (2004) Effect of ambient temperature and a prior neurotoxic dose of 3, 4-methylenedioxymethamphetamine (MDMA) on the hyperthermic response of rats to a single or repeated ('binge' ingestion) low dose of MDMA. Psychopharmacology 173:264–269

Green AR, Marsden CA, Fone KCF (2008) MDMA as a clinical tool: a note of caution. A response to Sessa and Nutt. J Psychopharmacol 22:929–931

Greene SL, Dargan PI, O'Connor N, Jones AL, Kerins M (2003) Multiple toxicity from 3,4-methylenedioxymethamphetamine ("ecstasy"). Am J Emerg Med 21:121–124

Hernandez-Lopez C, Farré M, Roset PN, Menoyo E, Pizarro N, Ortuno J, Torrens M, Cami J, de La Torre R (2002) 3,4-Methylenedioxymethamphetamine (ecstasy) and alcohol interactions in humans: psychomotor performance, subjective effects, and pharmacokinetics. J Pharmacol Exp Ther 300:236–244

Hiramatsu M, DiStefano E, Chang AS, Cho AK (1991) A pharmacokinetic analysis of 3,4-methylenedioxymethamphetamine effects on monoamine concentrations in brain dialysates. Eur J Pharmacol 204:135–140

Kolbrich EA Goodwin RS, Gorelick DA, Hayes RJ, Stein EA, Huestis MA (2008) Plasma pharmacokinetics of 3,4-methylenedioxymethamphetamine after controlled oral administration to young adults. Ther Drug Monit 30:320–332

Mas M, Farré M, de la Torre R, Roset PN, Ortuno J, Segura J, Cami J (1999) Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans. J Pharmacol Exp Ther 290:136–145

Mathúna BÓ, Farré M, Rastami-Hodjegan A, Yang J, Cuyas E, Torrens M, Pardo R, Abanades S, Maluf S, Tucker GT, de la Torre R (2008) The consequences of 3,4-methylenedioxymethamphetamine induced CYP 2D6 inhibition in humans. J Clin Psychopharmacol 28:523–531

McCann UD, Ricaurte GA (2001) Caveat emptor: editors beware. Neuropsychopharmacology 24:333–336

Mordenti J, Chappell W (1989) The use of interspecies scaling in toxicokinetics. In: Yacogi A, Kelly J, Batra V (eds) Toxicokinetics and new drug development. Pergamon, New York, pp 42–96

Morley-Fletcher S, Puopolo M, Gentili S, Gerara G, Macchia T, Laviola G (2004) Prenatal stress affects 3,4-methylenedioxymethamphetamine pharmacokinetics and drug induced motor alterations in adolescent female rats. Eur J Pharmacol 489:89–92

O'Shea E, Esteban B, Camarero J, Green AR, Colado MI (2001) Effect of GBR12909 and fluoxetine on the acute and long term changes induced by MDMA ("ecstasy") on the 5-HT and dopamine concentrations in mouse brain. Neuropharmacology 40:65–71

Ricaurte GA, Yuan J, Hatzidimitriou G, Cord BJ, McCann UD (2002) Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("ecstasy"). Science 297:2260–2263

Ricaurte GA, Yuan J, Hatzidimitriou G, Cord BJ, McCann UD (2003) Retraction. Science 301:1479

Sessa B, Nutt DJ (2007) MDMA, politics and medical research: have we thrown out the baby with the bathwater? J Psychopharmacol 21:787–791

Sessa B, Nutt DJ (2008) Reply to letter by Green Marsden and Fone (2007) about Sessa and Nutt's editorial (MDMA: baby with the bathwater). J Psychopharmacol 22:457–458

Upreti VV, Eddington ND (2007) Fluoxetine pretreatment effects pharmacokinetics of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) in rat. J Pharmaceut Sci 97:1593–1605

Valtier S, Phelix CF, Cody JT (2007) Analysis of MDMA and its metabolites in urine and plasma following a neurotoxic dose of MDMA. J Analyt Toxicol 31:138–143

Yang J, Jamei M, Heydari A, Yeo KR, de la Torre R, Farré M, Tucker GT, Rostami-Hodjegan A (2006) Implications of mechanism-based inhibition of CYP2D6 for the pharmacokinetics and toxicity of MDMA. J Psychopharmacol 20:842–849