Prediction of Human Lethality of Psychoactive Drugs From Rodent LD$_{50}$ Values

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ABSTRACT

The number of deaths from the abuse of psychoactive drugs is increasing year after year, and new designer psychoactive drugs of unknown toxicity frequently appear on the streets. Human lethal drug doses generally do not correlate well with animal LD$_{50}$ values. In order to investigate whether that holds for psychoactive drugs, human lethal dose values and rat and mouse LD$_{50}$ values for several routes of administration for eighteen such drugs were collected from the literature. Quantitative toxicity-toxicity relationship (QTTR) regression correlations of human and rodent lethal doses were poor for both rat and mouse oral and intraperitoneal lethal doses, but both rat and mouse intravenous LD$_{50}$ values correlated very well with human lethal doses (r2 = 0.823 and 0.756, respectively). Rat and mouse intravenous LD$_{50}$ values predicted from commercial software also correlated reasonably well with human lethal doses (r2 = 0.631 and 0.678, respectively). This means that it should be possible to use these correlations to predict the human lethal doses of new psychoactive drugs.

KEYWORDS

Correlation, Human Lethal Dose, Prediction, Psychoactive Drugs, Rodent LD$_{50}$

INTRODUCTION

A recent crime survey (Crime Survey for England and Wales, 2016/17) revealed that 19.2% of adults aged 16 to 24 had taken an illicit drug in the past year. According to the Office for National Statistics (Office for National Statistics), deaths related to drug poisoning in England and Wales are increasing year on year, from 2597 in 2012 to 3756 in 2017, an increase of 44.6%. Hence there is a need for the determination of lethal toxicity, based usually on animal experiments, for both medicines and drugs of abuse in order to obtain an estimation of safety and toxicity in humans.

It is acknowledged (Gable, 1993) that the determination of the human lethal dose (HLD) of a psychoactive substance is very difficult for a number of reasons, for example whether the substance is taken on its own or together with other substances, whether the person is a new or habitual user, whether the person is alone or in the company of others, and because of the sometimes marked interpersonal variability of rates of metabolism. Gable (1993) stated that 'the "best-guess lethal dose" for an average adult human who has not developed tolerance to the substance is probably the LD$_{50}$

extrapolated from a broad range of laboratory animal studies that falls within the range of lethality cited in clinical or forensic reports'.

The animal LD_{50} test was developed by Trevan (1927) for the biological standardization of drugs. Like HLD values, it cannot be considered as a biological constant, for it has been pointed out (Zbinden & Flury-Roversi, 1981) that it can vary with animal species, age, sex, weight, health, genetic variability, diet, method of administration, time of assessment after administration, ambient temperature, housing conditions (e.g. isolated or aggregated), time of day/night and time of year. It is therefore not surprising that correlations between animal LD_{50} and human toxicity values are generally poor (Abbott, 2005), although a few publications have reported modest results. For example, Hoffmann et al. (2010) found that human acute lethal doses of 30 chemicals correlated with rat oral LD_{50} values (coefficient of determination $(r^2) = 0.571$); Ekwall et al. (1998) found that human acute lethal doses of 50 chemicals (including a few psychoactive drugs) correlated reasonably well with rat and mouse oral LD_{50} values ($r^2 = 0.607$ and 0.653 respectively); Jover et al. (1992) reported correlations between HLDs of 10 chemicals with rat and mouse oral LD_{50} values (prediction errors 1.04 and 0.68 log unit respectively). Gable (2004) reported median HLD and range values for 20 commonly abused psychoactive substances; for example, he gave the median HLD for methadone as 100 mg, and the lethal range as 20 – 400 mg. He did not, however, examine possible correlations between human and animal lethal doses.

By far the most widely used animals in LD_{50} testing are rodents, especially rats and mice. It was therefore decided to examine correlations between HLDs and (following the suggestion of Gable (1993)) a range of rat and mouse LD_{50} values, with the aim of obtaining one or more valid animal models of human lethality of psychoactive drugs. Such models could then be used to predict the human lethality of new 'designer' drugs as they become available. The use of mean LD_{50} values in the present work hopefully means that many experimental errors and variations in their measurement were cancelled out.

Methods

Data

HLD values for 18 commonly abused psychoactive substances were taken largely from Gable (2004), who reported them for 20 such substances. However, two of those substances (isobutyl nitrite and nitrous oxide) are gaseous, with different dosage units, and so could not be included in the present study. Where Gable gave only a range of values together with an indication that the median value was '> X', a value only slightly greater than X was used; for example, for methamphetamine Gable (2004) gave the median value as > 150 mg, and the range as 140-1650 mg, so a value of 200 mg was selected as the HLD. Values were converted to mg/kg using a representative human weight of 68 kg (British National Formulary 2017-2018).

The 18 psychoactive drugs comprised examples of opioids, benzodiazepines, amphetamines, barbiturates, dibenzylcycloheptenes, morphinans, diphenylpropylamines, tryptamines, alcohols, carboxylic acids, phenoxyphenylpropylamines, diphenylpropylamines, arylcyclohexylamines, ergolines and dibenzopyrans; their actions included depressant, antidepressant, stimulant, hypnotic, sedative, antitussive, hallucinogenic, anesthetic and analgesic activities. This demonstrates the very wide applicability domain of the drugs used in this work.

The physicochemical applicability domain covered a logarithmic octanol-water partition coefficient (log P) range of –0.70 to 7.68, a pKa(base) range of 2.2 to 10.3, a pKa(acid) range of 1.0 to 9.6, and a logarithmic aqueous solubility (log S, with S in mmol/L) of –5.49 to 0.79, as well as ethanol which has infinite solubility in water.

A wide-ranging literature search was performed to find rat and mouse LD_{50} values obtained via oral, intraperitoneal, sub-cutaneous and intravenous administration, and arithmetic mean LD_{50} values were calculated, as has been done in previous studies (see, for example, Clothier et al., 1987; Hoffmann et al., 2010). Of the 144 endpoints, for only 28 (mostly involving subcutaneous

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