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Review

Tramadol deaths in Northern Ireland: A review of cases from 1996 to 2012

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ABSTRACT

In the UK tramadol is a frequently prescribed opioid analgesic which is becoming increasingly popular as a drug of misuse. Its use varies worldwide and in the last decade it has been upgraded to a controlled substance in several countries, due to an increased number of deaths associated with its use.

A review of all deaths associated with tramadol in Northern Ireland was performed and this highlighted 127 cases from 1996 to the end of 2012. A 10% increase in deaths due to tramadol was noted. In 2001 tramadol deaths represented 9% of all drug misuse deaths rising to 40% in 2011. The majority of the deaths occurred in males (62%), with a median age of 41 years, living in the Belfast city area (36%). Tramadol fatalities were found in combination with other drugs/medicines (49%), alcohol (36%) or alone (23%). Most of those who died did not reach hospital, with only 2% presenting with multi-organ or acute liver failure. In just over half of the deaths tramadol had not been prescribed by a medical practitioner (53%). Depression, addiction and seizures were recognised risk factors.

An increase in awareness of tramadol toxicity is needed amongst the public and doctors.

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1. Introduction

Tramadol was first introduced in Germany in the late 1970's.[1] Currently widely prescribed in the United Kingdom, it has yet to be classified as a controlled drug as defined by the Misuse of Drugs Act, 1971. Worldwide, tramadol's availability varies greatly. It can be freely purchased over the counter in Kuwait and Thailand without prescription. In the last decade Australia, Sweden and some states of America have changed their classification of tramadol to a controlled substance in response to an increased number of deaths associated with its use.

In recent decades, there has been an increase in the prescription of opioid analgesics and a rise in the use of addiction services by opioid addicts in the UK.[2,3] There is growing concern amongst some practitioners regarding the potential for an opioid epidemic similar to that seen in the United States of America.[4,5] However, despite a recent reduction in the overall number of opioid deaths in the UK, there continues to be an increase in tramadol prescriptions and number of tramadol related deaths.[2,6] The increase in tramadol prescriptions can largely be attributed to the phased withdrawal of co-proxamol (dextropropoxyphene and paracetamol) between 2005–2008.[7] Many practitioners believe that it has fewer risks including less potential for misuse, less dependence and fewer occurrences of respiratory depression than other opioids, as stated in the current edition of the British National Formulary.[8] The BNF does not, however, highlight the euphoric effects of tramadol, similar to those seen with morphine, heroin and oxycontin and as tramadol is more readily available than these controlled drugs, it is becoming an increasingly popular drug of abuse.

Tramadol is an opioid analgesic with similar effects to codeine.[9] It is a weak agonist at μ-opioid central receptors in the brain. Furthermore, tramadol also inhibits the re-uptake of noradrenaline and serotonin. In practice this is supported by only a partial reversal of its actions by naloxone, the opiate reversal agent used in the treatment of respiratory depression.[10]

Tramadol is well-absorbed orally and reaches its peak effects within 2 h and has a half-life of approximately six hours.[9] It is metabolised in the liver, by N- and O-demethylation via the cytochrome P450 pathway, followed by conjugation, before finally being excreted by the kidneys. The active metabolite, O-desmethlytramadol (M1), is largely responsible for tramadol's analgesic effects, and therefore toxic effects, as it has a significantly greater affinity for central opioid receptors than the parent drug.[11] Furthermore, any drug interactions with the cytochrome P450 enzymes, will therefore interfere with tramadol metabolism and alter its concentration in blood and tissue samples.[12]

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The side-effects of tramadol are varied with the most significant being neurological rather than cardiovascular. Symptoms are usually seen within four hours of ingestion.[10] Nausea, tachycardia and hypertension have been reported starting at doses of 500 mg.[10] At doses greater than 800 mg coma and respiratory depression may occur.[10] Respiratory depression, though uncommon, is more likely to arise when tramadol is taken in combination with alcohol or other central nervous system (CNS) depressants. Seizures are more common with tramadol than other opioids, occurring at doses as low as 200 mg.[13] The risk of seizures is greatest in those with a known seizure disorder.[14] The "serotonin syndrome" is another recognised side-effect of tramadol. This syndrome includes non-specific symptoms of agitation, tachycardia, confusion and hypertension.[15,16] These may occur with tramadol usage alone but are more likely to be fatal when taken in combination with other drugs which also increase serotonin activity particularly selective serotonin re-uptake inhibitors (SSRI's), mono-amine oxidase inhibitors (MAOI's) and tricyclic anti-depressants (TCA's).[14,15] Seizures and the serotonin syndrome are thought to be due to tramadol's ability to inhibit the re-uptake of serotonin and nor-adrenaline. These symptoms may also occur with other opioids which also weakly inhibit serotonin re-uptake (e.g. fentanyl, pethidine, methadone and dextromethorphan).[17] The lowest fatal dose reported to cause cardiac arrest and death was 5000 mg, between 12 and 50 times the daily dose.[18]

Side-effects may be more common in the elderly as they are more likely to be on numerous other medications.[14] In cases of suspected poisoning, measurement of blood tramadol levels in hospital is not usually carried out. The recommended management is supportive care. Most symptoms, if not life-threatening, usually resolve within 24 h.[13,14]

2. Methods

A review was performed of all autopsy reports in the State Pathologist's Department, Northern Ireland, where tramadol poisoning was included in the cause of death given by the pathologist. The case details were collected from the computerised Case Management System or retrieved from the archives. The total number of such deaths was 127 from 1996 to the end of 2012.

3. Results

The first death was reported in 1996. There has been a gradual increase in tramadol deaths during the last decade, from 2 cases in 2001 to 19 in 2012. The highest number occurred in 2011 when there were 23 deaths (Fig. 1).

In 2001 tramadol deaths represented 9% of deaths due to drug misuse in Northern Ireland. This rose to 40% in 2011 (Fig. 2).

More than half of the deaths were male (63% compared to 38% female). The average age at death was 41 years. The youngest death occurred in a fifteen year old girl and the oldest in an 80 year old female. The largest age group for male deaths was 21–30 years and for females 41–50 years. Overall the 41–50 age group gave the largest number of tramadol deaths (Fig. 3).

The majority of cases came from the Belfast area (36%), the capital city of Northern Ireland with a population of approximately 300,000 inhabitants. Outside of Belfast, the remaining province was split by healthcare sectors into north (24% of the cases), east (17% of the cases), south and west (each 10% of the cases) and 2% were from visitors (Fig. 4).

In the majority of cases death occurred at home or in the community. Only 8 patients (6%) reached hospital. Three of these hospital deaths were associated with multi-organ or liver failure.

In 24 cases (20%) tramadol was implicated indirectly or as a contributory factor in the cause of death. These deaths were principally due to aspiration pneumonia (17 cases). Others included drowning (2), positional asphyxia (1), bowel obstruction (1), congestive cardiac failure due to cardiomegaly (1), emphysema (1) and haemorrhage due to an incised radial artery (1).

Tramadol was prescribed in only 46% of cases (58), as recorded on the clinical summary provided at the time of autopsy. In 53% of the cases (67) tramadol was not prescribed and in 1% of cases (2) the source of the tramadol was unknown.

Only 29 deaths (23%) were due to ingestion of tramadol alone. In this group there was no variation in age or sex, however there was a higher percentage of apparently deliberate overdoses. The remaining deaths were due to tramadol in combination with other drugs and/or alcohol. Alcohol was associated with 36 deaths (28%). Tramadol was most commonly fatal when used in combination with one other drug, the most common being diazepam.

In 80 deaths (63%) there was a history of depression with a further 49 deaths (39%) admitting to previous overdose or self-harm. Sixty-three deaths (50%) were recorded as suffering with chronic pain, 52 deaths (41%) were known to abuse alcohol or drugs and 19 deaths (15%) had mental health problems. Only 7 cases (6%) had a diagnosis of epilepsy. One case had a witnessed seizure prior to death, which was associated with a fatal level of tramadol in

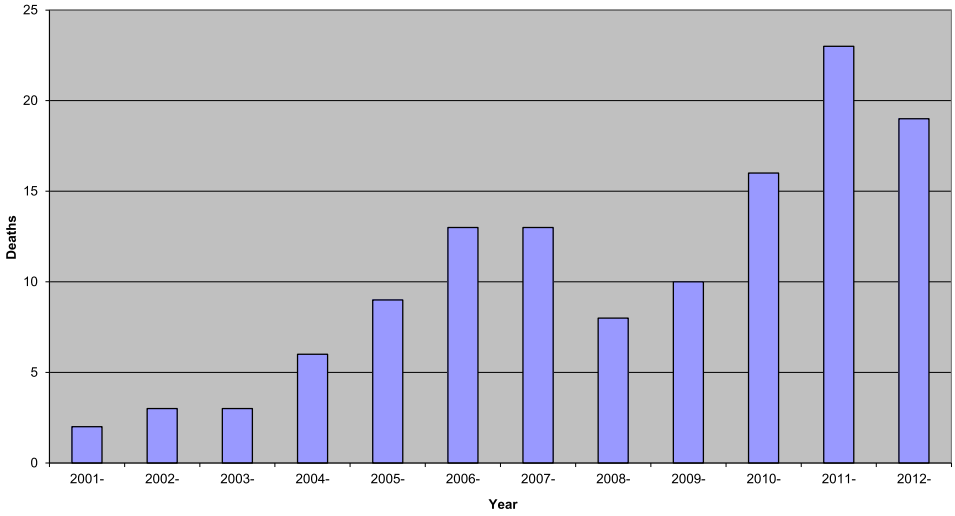

Fig. 1. Total number of tramadol deaths per year from 2001 to 2012.

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