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Rhabdomyolysis and acute renal failure resulting from alcohol and drug abuse

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Summary

Rhabdomyolysis is a common cause of acute renal failure (ARF) associated with drug misuse. Abuse of the gel formulation of temazepam has been a particular problem in the West of Scotland. We performed a retrospective review of dialysis-dependent ARF from rhabdomyolysis and drug misuse in the West of Scotland, 1986–1997. We identified 76 patients, of whom 87% were male. Seventeen cases occurred in the first 6 years, compared with 59 in the subsequent 6 years. Median age was 32. Thirty cases followed intravenous drug misuse, 46 followed oral drug misuse. The substances most frequently misused were alcohol (54%), heroin (24%) and parenteral temazepam (17%). The temazepam cases all followed the introduction of the gel formulation. Three out of 4 patients requiring limb amputation had injected temazepam. Of intravenous drug misusers tested, 72% were hepatitis-C-positive. Some 43% of patients had deprivation scores in the worst category. ARF due to rhabdomyolysis from substance misuse is increasing in our area. Alcohol is frequently responsible. The introduction of the gel formulation of temazepam has contributed to the increase. Those at risk in this study were young, male, had a high incidence of hepatitis C and lived in the most deprived areas.

Introduction

Rhabdomyolysis is a common cause of acute renal failure associated with drug abuse. The most frequently-recognized substances responsible are alcohol and intravenous opiates.[1] Acute hospital admissions in Greater Glasgow due to alcohol and drug misuse have risen steeply over the last 10 years, and it was our impression that the incidence of acute renal failure from rhabdomyolysis following drug abuse had also substantially increased. Parenteral abuse of temazepam in the West of Scotland was first reported in 1987.[2] In an attempt to discourage intravenous abuse, the formulation of temazepam was changed from a liquid to a hard gel in November 1989. Unfortunately this compounded the problem, with misusers liquefying the preparation on a heated metal spoon and then injecting the fluid into an accessible vessel. Subsequently, two cases of acute renal failure from rhabdomyolysis resulting from injection of these liquefied 'jellies' have been reported.[3] In light of the evidence of temazepam misuse, legislation was introduced to ban prescription of the gel formulation in January 1996. Our experience of this problem has prompted us to carry out a review of acute renal failure associated with rhabdomyolysis and drug abuse with particular emphasis on those cases resulting from parenteral temazepam.

Methods

We retrospectively reviewed all discharge summaries from January 1986 to the end of December 1997 in the three renal units in Glasgow. This was complemented by a search of the renal unit databases in the Royal and Western Infirmaries. The three renal

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units together serve a population of just under 2 million. All patients with acute renal failure due to rhabdomyolysis which was associated with drug overdosage or substance abuse, and who required dialysis were included. In all cases, it was the opinion of the clinician responsible that the acute renal failure was either entirely or partly a result of rhabdomyolysis. Patients were divided according to the route of drug administration (intravenous or oral). If patients had taken alcohol along with intravenous drugs, they were included in the intravenous drugs abuse group.

Results

A total of 76 patients with substance abuse and acute renal failure associated with rhabdomyolysis who required dialysis were identified. Sixty-six were male and ten female. The median age was 32 years (range 20–66). Thirty were intravenous drug abusers and 46 took drugs orally. The median age of the intravenous drug abusers was markedly lower, at 29 years (range 21–37) compared with 40 years (20–66) in those taking drugs orally ($p<0.0001$, 95% CI -21 to -8, Mann Whitney). The median time spent in the renal unit was 19 days (intravenous 20, oral 18), with a median of 12 days (intravenous 14, oral 11) during which dialysis was required. Thus over the 12 years of the study, a total of 0.33 beds each day were taken up by patients with acute renal failure secondary to substance abuse. There was no difference between intravenous and oral drug abusers in time to recovery of function or length of stay in a renal unit.

Table 1 shows the main substance(s) abused by each patient. Fifty-three patients had abused one drug, 15 two, and eight more than two. Figure 1 shows the number of patients presenting per year and the relative contribution from intravenous and oral drug misuse. There has been a substantial increase in the annual incidence of acute renal failure secondary to rhabdomyolysis and drug abuse. This has increased from 3–4 cases per annum before 1990 to 11–12 cases per annum in the last 2 years of the study. This has resulted from increases in both intravenous and oral drug abuse. Alcohol was the most commonly abused substance, being implicated in 54% of cases, however, amongst those secondary to intravenous drug abuse, temazepam had been injected in at least 43% of cases (one unknown). A number of patients had injected a combination of opiates and temazepam. All the cases of temazepam-related rhabdomyolysis occurred after the introduction of the hard gel formulation at the end of 1989 (Figure 2). Following withdrawal of the gel preparation, it can be seen that parenteral temazepam injection was responsible in only two cases in 1996, with no documented cases in 1997.

Table 2 shows the likely cause of the rhabdomyolysis. Pressure necrosis of muscle due to prolonged coma or a compartment syndrome was the commonest mechanism, but ischaemic necrosis from direct intra-arterial injection was thought to be the main factor in at least 9 of the 13 patients who had injected temazepam. Fifteen of the 76 patients (20%) required ventilation and admission to intensive care units. Mortality was low (two deaths), but morbidity amongst the intravenous drug abusers was high, especially in those injecting temazepam. Of the 13 patients in whom injecting temazepam was responsible, three required amputation (1 arm, 1 leg, 1 toes) and a further three were left with significant functional residual deficit (upper and lower limb nerve palsies), giving a morbidity of 46% in this group. Only one amputation (below knee) was required in the other 64 patients, although a further 29% were left with residual muscle or limb weakness. Fifteen patients (20%) at presentation to the renal unit had life-threatening hyperkalaemia (serum K^+ >6.5 mmol/l). Fifty of the 76 patients (66%) needed to commence haemodialysis on the day of admission to the renal unit, with a further 18 patients (24%) treated with haemodialysis within 24 h of admission.

There were no HIV-positive patients and only one patient was surface-antigen-positive for hepatitis B. However the incidence of hepatitis C was noted to be high amongst those patients injecting drugs.

Table 1 Main substance(s) abused

Substance(s) abused	Number
Alcohol	41
Heroin (parenteral)	18
Temazepam (parenteral)	13
Benzodiazepines (oral)	10
Major tranquillizers	5
Methadone	4
Other parenteral opiates	3
Antidepressants	3
Others	11

Table 2 Cause of the rhabdomyolysis

Suspected cause of rhabdomyolysis	Number of patients
Pressure necrosis or ischaemic necrosis	59
Prolonged seizures	9
Alcohol toxicity	2
Hypothermia	1
Cardiac arrest	1
Unknown	4

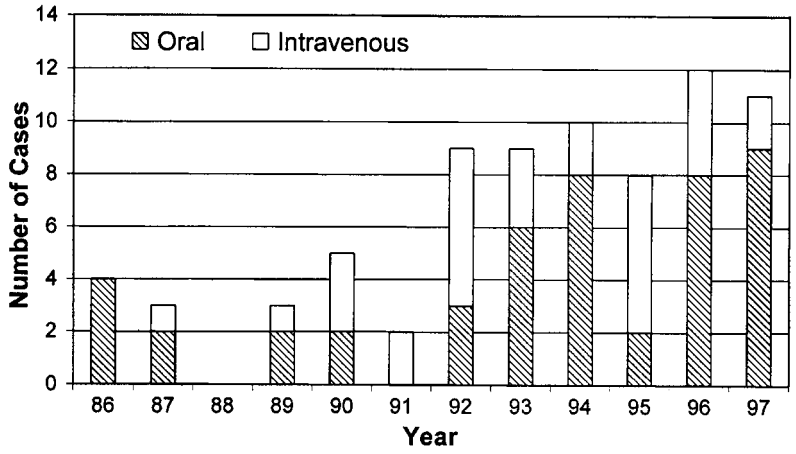

Figure 1. Annual incidence of acute renal failure and rhabdomyolysis: intravenous vs. oral drug misuse.

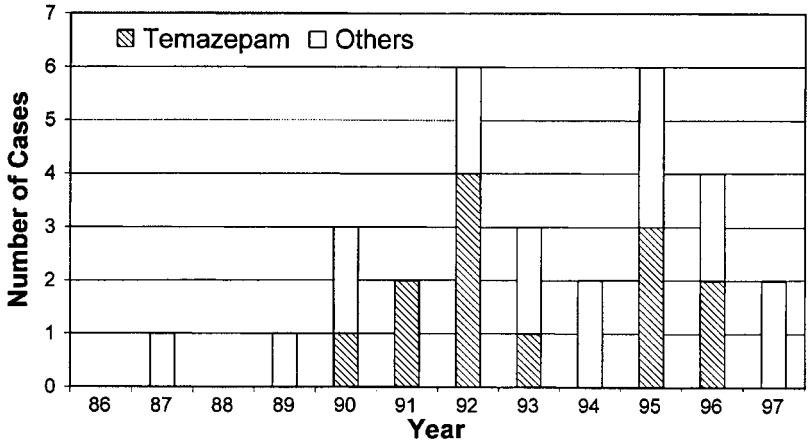

Figure 2. Annual incidence of acute renal failure and rhabdomyolysis from intravenous drug misuse: temazepam vs. others.

Routine testing for hepatitis C has been available since 1990, and since then, 28 patients have had rhabdomyolysis and acute renal failure from intravenous drug abuse. Of these, 18 have been tested for hepatitis C, with 13 positive and only five negative results.

The deprivation category for each patient, based on the 1991 Carstairs deprivation scores, was obtained for each patient according to their postcode. The patients were then classified according to their deprivation category, from 1 (affluent) to 7 (deprived) (Figure 3). Some 43% of the patients were in the most deprived category, with no patients in the most affluent category.

Discussion

In this study we have found more patients with acute renal failure and non-traumatic rhabdomyolysis associated with substance abuse than has previously been described in a single report, suggesting that the incidence of rhabdomyolysis-related acute renal failure secondary to substance abuse has increased, at least in our area. Temazepam abuse has not only contributed to this increase but has been the causal agent in a high percentage of intravenous drug abusers.

The renal units at Glasgow's Royal and Western Infirmaries and Stobhill General Hospital serve a population of just under 2 million, and their catchment area during this period has included most of the West of Scotland. The true incidence of rhabdomyolysis from substance abuse, and the percentage of these patients who develop renal dysfunction, is unknown. However the incidence of dialysis-dependent acute renal failure from rhabdomyolysis due to substance abuse in this 12-year period has increased markedly from 17 cases in the years 1986–1991 to 59 cases in the next 6 years. This rise has occurred despite a fall in the catchment area following the creation of two renal units in nearby district general hospitals in the late 1980s. It is very unlikely that the increased number of patients could represent an increased referral rate, in view of the young age of almost all the patients with this type of acute renal failure, also the search of discharge summaries was just as detailed in the earlier as in

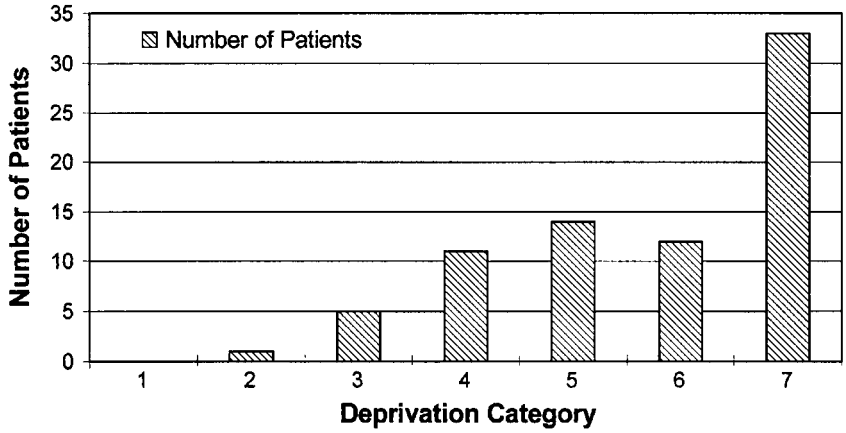

Figure 3. Deprivation category of patients with rhabdomyolysis from alcohol and drug misuse.

the more recent years. The increase in incidence reflects the general increase in hospital admissions secondary to drug or alcohol misuse over the same time period (Dr L. Gruer, Greater Glasgow Health Board, personal communication).

The increase in rhabdomyolysis and acute renal failure is likely to be due not only to the increased parenteral abuse of drugs but also the introduction of the gel formulation of temazepam. First reports of intravenous abuse of temazepam came from Glasgow in 1987.[2] The clear liquid from the capsules was easy to inject and gave the user a 'buzz'. In November 1989 the formulation of temazepam was changed to a hard gel in an attempt to discourage misuse. Addicts however circumvented this problem by heating the 'jellies' on a metal spoon and then injecting the melted substance into an accessible blood vessel. Subsequently a number of reports of ischaemic limbs after intra-arterial injection of temazepam were published,[4,5] and in 1994 Jenkinson reported two cases of rhabdomyolysis and acute renal failure following intra-arterial injection of temazepam.[3] All 13 cases reported here occurred after the change in formulation of the temazepam and this change appears to have contributed to the increased incidence of acute renal failure from rhabdomyolysis. It is noteworthy that following the introduction of legislation banning the prescription of the gel formulation in 1996, there have been only two cases involving parenteral temazepam, with no cases in the final year of the study.

The young median age of these intravenous drug abusers (29 years) is likely to reflect the mean age of intravenous drug abuse in the community. The high morbidity in this group was very striking, especially in those injecting temazepam. The patients with complications from intra-arterial temazepam injection tended to present early with painful, mottled limbs due to the effect of temazepam on the arterial supply and subsequent ischaemic myonecrosis. The ischaemia is thought to result from a toxic effect on endothelial cells leading to arterial, capillary and venous thrombosis.[6] In contrast, the majority of patients developed rhabdomyolysis from prolonged unconsciousness and immobility leading to compartment syndromes and pressure necrosis, rather than from a direct toxic effect of the substance abused. These patients tended to present later, a point illustrated by the fact that 66% of the patients needed haemodialysis on the day of admission to a renal unit.

This report has not detailed aspects of conservative management of rhabdomyolysis and acute renal failure. Only patients receiving haemodialysis were studied, therefore the population represents the severe end of the spectrum of renal injury from rhabdomyolysis. It was not possible to determine the extent to which active treatment of rhabdomyolysis with either intravenous bicarbonate or forced alkaline-mannitol diuresis was used, as bicarbonate was also used to treat hyperkalaemia. Also, many of the patients studied pre-1990 received dopamine and mannitol as standard treatment for all cases of acute tubular necrosis. However, there is no clear evidence that a mannitol-induced diuresis is more effective than a saline diuresis in rhabdomyolysis,[7] and no patient in the later years of the study was treated with mannitol.

Despite widespread concern about the presence of HIV in the drug-abusing population, no patients in this study were HIV-positive. This is not surprising, as Glasgow is known to have a low prevalence of HIV infection.[8] However hepatitis C was common in our patients with rhabdomyolysis following intravenous drug misuse (72% of those tested), and corresponds to the published data of hepatitis C seropositivity in intravenous drug abusers in the UK, where the overall prevalence is thought to be 80%.[9] Not only does this pose a further long-term risk to the health of these individuals, but it also represents a hazard both to the medical and nursing staff who have to care for and dialyse these patients, and to the other in-patients, due to the possibility of noso-

comial spread of the virus.[10] Previous reports of non-traumatic rhabdomyolysis have emphasized the high survival of those with acute renal failure[1,11] and our study confirms this, with a mortality of 2.6%. However, these patients have a high morbidity, especially when one considers the young average age of this group. Added to this is the widespread incidence of hepatitis C carriage with its as yet undetermined long-term effect on the liver.

Drug misuse, particularly parenteral drug abuse, is commonest in socially deprived areas of cities. The deprivation scores obtained show that the majority of our patients with acute renal failure resulting from rhabdomyolysis and drug abuse lived in the poorest areas of the West of Scotland, with 43% of patients living in the most deprived category. This compares with data for the whole of Scotland, where 7% of the population are in category 7.[12] The implication of this finding is that primary and secondary prevention along with health education may have a limited impact on the incidence of acute renal failure from drug abuse and rhabdomyolysis, as they are often less successful in areas of severe socio-economic deprivation. The withdrawal of the gel formulation of temazepam should have a beneficial effect on the incidence of rhabdomyolysis, and the absence in our series of any cases in the final year is encouraging. The beneficial effect of methadone programmes[13] may also help to reduce the number of cases linked to intravenous drug abuse. Medical care is clearly successful in treating the acute problem, but whether prevention can be successful without significant socio-economic improvement remains to be established.

In conclusion, in our area the incidence of acute renal failure secondary to rhabdomyolysis resulting from substance abuse is clearly increasing. The population injecting drugs seems to be significantly younger than those involved in oral substance abuse, and the majority live in areas of severe socio-economic deprivation. The change in formulation of temazepam, which was designed to discourage misuse, has contributed to this increase and has been associated with a high morbidity. With the continued increase in substance abuse in general and alcohol in particular, a continuing high number of cases of acute renal failure from non-traumatic rhabdomyolysis is to be expected.

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