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Toxicity of norpethidine in sickle cell crisis

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Over six months we observed eight episodes of focal and generalised seizures in patients with sickle cell disease who had been treated with high doses of intramuscular pethidine. Recently Mitchell *et al* reported the death during grand mal seizure of a man in sickle cell crisis after two days of taking high dose pethidine.[1] Norpethidine, an N-demethylated metabolite of pethidine, was identified as neurotoxic by Batterman in 1957, and subsequent studies have documented the adverse consequences of norpethidine accumulation.[2 3] Although isolated norpethidine concentrations have been measured at random in patients with sickle cell disease, we have found no systematic study. Our objective was to measure serum pethidine and norpethidine concentrations after multiple doses of pethidine to assess the extent of their accumulation and to identify their relation with seizures.

Patients, methods, and results

Fourteen AfroCaribbean patients with a diagnosis of sickle cell crisis who were receiving two hourly intramuscular pethidine gave verbal consent to give blood for analysis. Blood was taken immediately before and 15, 30, 60, and 120 minutes after a pethidine injection. The patient's weight, serum urea and creatinine concentrations, most recent individual dose of pethidine, total dose in the previous 24 hours per kilogram body weight (24 hour pethidine dose), and total dose of pethidine during the crisis (total dose) were noted. Two additional patients who suffered grand mal seizures while receiving high dose pethidine treatment had blood samples taken shortly after the convulsions. Pethidine and norpethidine concentrations were measured by gas chromatography.[4]

Nine men and seven women of mean age 27 years (range 17-45) and mean weight 59 kg (range 50-70) were investigated. They had received two hourly intramuscular pethidine for between one and 35 days (mean seven, mode three). All except one had detectable concentrations of pethidine and norpethidine in the first sample. Mean (range) pharmacokinetic data for pethidine and norpethidine were: maximum measured plasma concentration 1·29 (0·46-2·8) and 0·72 (0·24-1·86) µg/ml; time to maximum concentration 37·5 (12-120) and 55 (15-120) min; area under the curve of concentration against time curve 109 (20·5-243) and 66·2 (18-100) µg.s/ml. Maximum measured concentrations of norpethidine exceeded 1 µg/ml in four patients, three of whom had suffered a

convulsion within a few hours of sampling. Two of these patients had been taking pethidine tablets at home before admission, and one had significant renal impairment (serum creatinine concentration 146 µmol/l, normal range 50-100).

Linear regression analysis showed that the maximum measured concentration (figure) and area under the time concentration curve for norpethidine correlated significantly with the 24 hour pethidine dose ($r=0·74$, $p=0·001$ for both). The relation was also significant for pethidine ($r=0·56$, $p<0·05$ for both). There was no
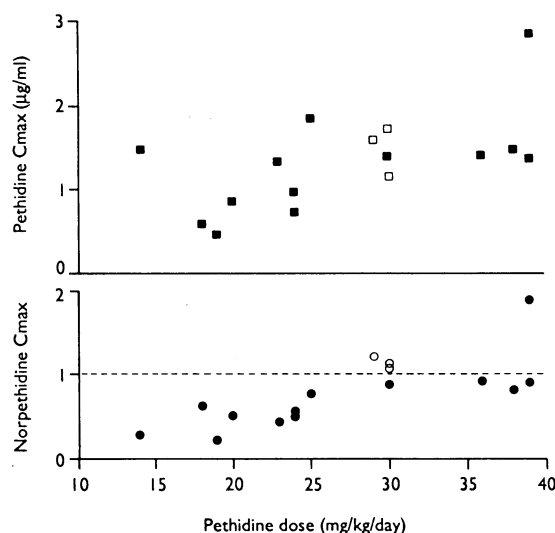
Maximum measured concentration of pethidine (square symbols) and norpethidine (round symbols) after intramuscular pethidine plotted against daily dose of pethidine in 16 patients. Open symbols represent the three patients who had convulsions

association between peak plasma pethidine concentration and seizures. There was no correlation between the total dose or last dose of pethidine and the maximum measured concentration or area under the time concentration curve for pethidine and norpethidine.

Comment

The results suggest that daily doses of pethidine greater than 25 mg/kg may be associated with toxicity (figure), particularly in the presence of renal impairment or if pethidine has been taken orally, when high first pass clearance results in rapid conversion to norpethidine. As the life expectancy of sickle cell patients increases, renal impairment becomes a more significant problem in older patients. The plasma half life of norpethidine with normal renal function is 14-20 hours, which implies that norpethidine concentrations may take about three days to reach 90% of the final plateau value. As all but one of our patients had been receiving pethidine for three days or more, no correla-

tion between total pethidine dose and norpethidine concentration was found. In renal impairment nor-pethidine elimination is prolonged, leading to a greater accumulation.[5]

Despite mounting evidence against pethidine as a first line analgesic in sickle cell crisis its use persists. We find that patients seem to prefer intramuscular pethidine despite its short duration of action and poor analgesia. This preference was also stated by patients' representatives (Sickle and Thalassaemia Association of Counsellors, Cardiff, September 1991). Apparent ease of administration and doctors' familiarity with the drug further perpetuates this legacy. Pethidine should not be used in patients who have a history of seizure

after pethidine or renal impairment.[2 3] Daily doses exceeding 25 mg/kg are likely to produce excitatory effects due to norpethidine toxicity.

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Prevalence of potential pathogens in cervical canal before termination of pregnancy

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Pelvic infection is a complication of termination of pregnancy.[1] The risk is increased if Chlamydia trachomatis or other potential pathogens are present in the cervical canal before the abortion.[2] We report the prevalences of five potential pathogens in the cervical canal of women requesting terminations in Sheffield.

Patients, methods, and results

We performed a retrospective analysis on the microbiological results of endocervical swabs taken from 1784 consecutive women requesting termination of pregnancy at this hospital. Neisseria gonorrhoeae was isolated from three women, C trachomatis from 155, Mycoplasma hominis from 315, Ureaplasma urealyticum from 340, and Trichomonas vaginalis from 30. One or more of these micro-organisms were isolated in 652 women.

For the analysis, if either N gonorrhoeae or C trachomatis was isolated the patient was deemed to be at a "high risk" of developing pelvic infection after termination whereas those harbouring M hominis, U urealyticum, or T vaginalis were thought to be at "moderate risk." As marital status, age, and parity are likely to be related to risk a multivariate approach was taken. A cumulative logic model[3] was fitted to the data with the SAS statistical package with the dependent variable as infection (none, moderate risk, high risk) and the explanatory variables as marital status (single, married, divorced, or separated), age (≤24, 25-29, 30-34, ≥35), and parity (primigravid, nulliparous other than primigravid, multiparous).

The model of best fit included all three of the explanatory variables; the fit became significantly poorer (at the 5% level) when any of these variables was dropped from the model. The final model showed that

the chance of being at high risk of pelvic infection was increased for single women (adjusting for age and parity), those aged under 25 (adjusting for marital status and parity), and multiparous women (adjusting for marital status and age).

Comment

This large study showed that potential pathogens are found in the endocervical canal of an appreciable proportion of women requesting termination of pregnancy in Sheffield, thereby supporting the findings of other small studies in the United Kingdom.[4] It also confirmed that such micro-organisms are more frequently isolated from young single women.

If C trachomatis was present in the cervical canal before termination there was a 20-25% risk of the woman developing postabortion pelvic infection.[2] This would have caused the woman discomfort and distress and might have required a further admission to hospital. A few of these women would experience long term subfertility and pelvic pain.[5] Screening every patient requesting a termination would add about £8.00 to the cost of each abortion. However, the cost of treating women with established postabortion infection and of the long term sequelae should be set against this. Furthermore, by identifying infected women their partners can be tested and if necessary treated, thereby reducing the chances of the woman being reinfected and the pool of infected subjects within the population.

As cervical infections are more common in certain groups it would be possible to introduce selective screening to reduce the costs. The table illustrates the sensitivity and efficiency of different policies. If all single women under the age of 25 were tested only 60% of the population would be screened but 73% of infected subjects would be detected. Furthermore, most patients for whom subsequent fertility is most important would be screened.

We recommend that all patients requesting termination of pregnancy are screened for potential endocervical pathogens and that when these are detected appropriate antibiotics are prescribed at the time of the abortion. If resources are limited a selective policy could be introduced.

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Sensitivity* and efficiency† of selective testing for endocervical micro-organisms before termination of pregnancy

Patient characteristic	No (%) women tested	High risk infections		All infections	
		Sensitivity (%)	Efficiency (%)	Sensitivity (%)	Efficiency (%)
All women	100·0	100·0	1·00	100·0	1·00
Single	71·1	82·8	1·16	78·8	1·11
Multiparous	43·3	39·2	0·90	40·1	0·92
Aged <25 years	66·2	77·7	1·17	72·1	1·09
Single, multiparous	16·9	21·6	1·28	20·5	1·21
Single, aged <25 years	59·7	72·6	1·22	67·3	1·12

★Sensitivity=No detected/No infected×100.   †Efficiency=sensitivity/percentage of patients tested.