High-dose antipsychotic medication

Improving clinical practice in a psychiatric special (intensive) care unit

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We audited the use of high-dose antipsychotic drugs in patients admitted to a special (intensive) care unit over two periods. Five out of 57 patients in the first sample and three out of 62 in the second were treated with a single antipsychotic drug above the *British National Formulary* maximum dose. The proportion of patients treated with antipsychotic drugs such that the total dose in chlorpromazine equivalents was greater than 1000 mg, fell. The audit showed improvements in clinical practice, particularly with respect to the onset of, indication for and outcome of high-dose treatment and in monitoring the patients' physical status.

There has been concern recently about the use of antipsychotic drugs in doses above those recommended in the *British National Formulary* (*BNF*; Joint Formulary Committee, 1994). Reports have demonstrated the risk of severe side-effects, behavioural disturbance and perhaps sudden death related to higher drug dosage (Barnes & Bridges, 1980; Bollini *et al*, 1984; Baldessarini *et al*, 1988; Mehtonen *et al*, 1991). In response to this unease the Royal College of Psychiatrists convened a panel of experts to give an authoritative opinion on the use of high doses (Thompson, 1994). They considered that it was unlikely that high-dose treatment was always fully justified and offered guidance on precautions to be taken when prescribing antipsychotics in doses which exceed the *BNF* recommended maximum.

Audits of the use of high-dose antipsychotic medication in the UK have used the method described by Edwards & Kumar (1984), that is gathering data on prescribing on a single census day (Fraser & Hepple, 1992; Gill, 1993; Stanley & Doyle, 1993). This may underestimate the number of patients who will receive high-dose medication at some time during a hospital admission. We aimed to describe the characteristics of all patients who had received high-dose treatment in a special (intensive) care unit, to survey the record keeping of high-dose treatment episodes and to complete the audit cycle after discussion on the unit as to how the Royal College recommendations could be implemented.

The study

The survey was carried out in a 17-bed special (intensive) care unit which provides a locked facility for disturbed patients in Newcastle upon Tyne. The case notes of all patients admitted between 1 April 1993 and 31 March 1994 were examined. Data was gathered from prescription sheets, discharge summaries and case notes. A local protocol for the use of high-dose treatment was developed following publication of the Royal College of Psychiatrists' *Consensus Statement* (1993). This covered the issues of reviewing diagnosis and treatment, getting consent, recording information, medical review and outcome and was for use with any patient receiving higher doses of antipsychotics. The protocol treatment sheet is set out in Table 1. To complete the audit cycle, the case notes for the same number of admissions admitted after 1 September 1994 were examined.

An episode of high-dose treatment was defined as a period of more than one day in which a single antipsychotic drug dose exceeded the *BNF* recommended maximum or where the combined daily dose in chlorpromazine (CPZ) equivalents was greater than 1000 mg. The CPZ equivalent doses in the *BNF* and other published guidelines vary considerably for oral and depot drugs. The figures we used (Table 2) are inevitably arbitrary and were derived from the *BNF*, Rey *et al* (1989) and Schulz *et al* (1989).

The case notes of patients who had an episode of high-dose treatment during an admission were surveyed using 15 indicators of good practice derived from the Royal College of Psychiatrists' guidelines (Thompson, 1994) covering the initiation, monitoring and outcome of the use of high-dose treatment (Table 3) with a positive record

scoring one point. In addition, the raters went on to make an assessment of the indication for treatment in each episode (emergency sedation, acute antipsychotic treatment, long-term management of treatment resistant schizophrenia, unclear or not indicated).

Findings

There were 76 admissions involving 63 patients in each sample, of which 57 patients in the first sample and 62 patients in the second were treated with antipsychotic medication. Patient and admission characteristics are shown in Table 4. There were no significant differences between the two samples in terms of age, ethnicity, diagnosis and length of stay, although there were fewer females in the second sample.

Five out of 57 patients in the first sample and three out of 62 in the second sample were treated with a single antipsychotic drug above the *BNF* maximum dose. There was a reduction between the first and the second survey in the number of patients treated with drugs such that the total

Table 1. High-dose antipsychotic treatment sheet

Date					
Name					
Age, gender					
Diagnosis					
Date of admission					
Drugs prior to admission and current medication					
Current mental state and physical state (abnormal findings)					
Review of diagnosis and treatment					
Indication for high-dose treatment	1		2	3	
(1=emergency sedation, 2=acute antipsychotic treatment, 3=long-term management of treatment resistant schizophrenia)					
Consent for high-dose treatment	1		2	3	
(1=yes, 2=no, 3=S58)					
New doses initiated					
Total chlorpromazine equivalent dose					
Review at one week			date:		
Physical examination or observation			yes	no	
ECG			yes	no	
FBC, U & E			yes	no	
One week outcome	1	2	3	4	5
(1=much worse, 2=worse, 3=no change, 4=better, 5=much better)					
Adverse effects			yes	no	
If yes – record what and action taken					
Dose changes					
Review at one month			date:		
Physical examination or observation			yes	no	
ECG			yes	no	
FBC, U & E			yes	no	
One month outcome	1	2	3	4	5
(1=much worse, 2=worse, 3=no change, 4=better, 5=much better)					
Adverse effects			yes	no	
If yes – record what and action taken					
Dose changes					
Review at three months or at end of treatment			date:		
Physical examination or observation			yes	no	
ECG			yes	no	
FBC, U & E			yes	no	
Three month outcome	1	2	3	4	5
(1=much worse, 2=worse, 3=no change, 4=better, 5=much better)					
Adverse effects			yes	no	
If yes – record what and action taken					
Reduce dose to normal			yes	no	
If no – why not					

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Table 2. Chlorpromazine (CPZ) dose equivalent and *BNF* advisory maximum daily doses

	CPZ equivalent dose		*BNF* maximum dose	
Chlorpromazine	500 mg		1000 mg	
Clozapine	250 mg		900 mg	
Droperidol	20 mg		120 mg	
Haloperidol	10 mg		100 mg (rarely 200 mg)	
Loxapine	50 mg		250 mg	
Pimozide	10 mg		20 mg	
Remoxipride	250 mg		600 mg	
Risperidone	10 mg		16 mg	
Sulpiride	1000 mg		2400 mg	
Thioridazine	500 mg		800 mg	
Trifluoperazine	25 mg		none	
Zuclopenthixol (oral)	100 mg		150 mg	
Flupenthixol decanoate	40 mg	2 weekly	400 mg	weekly
Fluphenazine decanoate	25 mg	2 weekly	100 mg	2 weekly
Haloperidol decanoate	100 mg	4 weekly	300 mg	4 weekly
Pipothiazine palmitate	25 mg	2 weekly	200 mg	2 weekly
Zuclopenthixol decanoate	200 mg	2 weekly	600 mg	weekly

CPZ equivalent dose was greater than 1000 mg (29/57 *v.* 18/62, χ^2=5.9, d.f.=1, *P*=0.02).

In the first sample, patients on high doses were more likely to have a diagnosis of schizophrenia (21/29 *v.* 8/28, χ^2=11.0, d.f.=1, *P*<0.001). They were also more likely to be treated with more than one antipsychotic agent (27/29 *v.* 5/28, χ^2=32.8, d.f.=1, *P*<0.0001). There was no such relationship with age, gender, ethnicity or length of stay.

In the second sample, the findings were similar, except that there was no association between high-dose treatment and a diagnosis of schizophrenia (7/18 *v.* 17/44, χ^2=0.003, d.f.=1, *P*=1.0). The effect for polypharmacy was again significant (17/18 *v.* 3/44, χ^2=44.9, d.f.=1, *P*<0.0001).

There were 36 episodes in the first sample and 22 in the second in which high-dose treatment was given. Data were collected on 34 out of 36 episodes and 21 out of 22 episodes respectively. The maximum score was 15 and the mean scores improved from 8.1 (s.d.=2.0) to 10.0 (s.d.=3.0), (*t*=2.8, d.f.=53, *P*=0.007) between the first and second study. There were significant improvements in four good practice indicators: record of initiation of treatment, record of indication for treatment, assessment of physical status and record of outcome (see Table 3).

Adverse events were recorded in six out of 12 treatment episodes in the first sample and nine out of 10 episodes in the second, in which the

Table 3. Change in number (%) of case notes recording information on good practice indicators between the first and the second study

Indicator of good practice	Study I *n*	%	Study II *n*	%	χ^2	*P*
Record of patient's mental state	34	100	21	100	–	–
Record of weekly review of treatment	34	100	21	100	–	–
Initiation of treatment by a senior	32	94	20	95	Fisher	1.00
Dose increases not less than weekly	32	94	21	100	Fisher	0.52
No contraindications to treatment	31	91	21	100	Fisher	0.28
Record of team decision	29	85	20	95	Fisher	0.39
Dose reduction at three months	26	76	13	62	1.34	0.25
Record of adverse effects	12	35	10	48	0.82	0.36
Record of outcome	11	32	15	71	**7.95**	**0.005**
Record of other options explored	8	24	10	48	3.42	0.06
Record of indication for treatment	7	21	10	48	**4.44**	**0.04**
Record of physical assessment	7	21	11	52	**5.96**	**0.01**
Routine blood tests done	7	21	7	33	1.11	0.29
ECG done	3	9	4	19	Fisher	0.41
Record of initiation of treatment	1	3	5	14	Fisher	**0.03**

Figures in bold are of significant value

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Table 4. Patient characteristics

	Study I	Study II
Admissions	76	76
Patients	63	63
on antipsychotics	57 (100)	62 (100)
High-dose treatment		
yes	29 (51)	18 (29) (χ^2=5.9, d.f.=1, **P=0.02**)
no	28 (49)	44 (71)
Gender		
male	41 (72)	55 (89) (χ^2=5.4, d.f.=1, **P=0.02**)
female	16 (28)	7 (11)
Diagnosis		
schizophrenia	29 (51)	24 (37) (χ^2=1.8, d.f.=3, P=0.61)
related psychoses	11 (19)	15 (24)
mood disorders	12 (21)	17 (27)
other disorders	5 (9)	6 (10)
Mean age/years	35.5	33.5 *t*-test (*t*=1.0, d.f.=117, P=0.32)
Median length of stay/days	28.0	27.5 Mann–Whitney *U* test (*z*=−1.25, P=0.21)

Figures in bold are of significant value

presence or absence of adverse effects was noted. Thirteen of these were commonly recognised side-effects – Parkinsonism, akathisia, dystonia, oversedation and postural hypotension – and chlorpromazine was the drug most frequently implicated. One patient (in the first sample) developed neutropenia while on a combination of chlorpromazine 600 mg daily, zuclopenthixol depot 600 mg twice weekly, lorazepam 6 mg daily and sodium valproate 600 mg daily. This patient had previously had an episode of neutropenia while being treated with clozapine. Two patients had previously had neuroleptic malignant syndrome and these were the treatment episodes where it was recorded that there was a contra-indication to high-dose treatment.

In the first sample, the perceived indication for high-dose treatment was acute antipsychotic treatment in 20 episodes, long-term management of treatment resistant schizophrenia in six, emergency sedation in three, unclear in two, and not indicated in three. In the second, the indications were acute treatment 15, long-term management in two, sedation in one, and unclear in two.

Comment

There are numerous guidelines for the use of antipsychotic drugs in high-doses, but all recognise that the notion of high-dose is arbitrary (Baldessarini *et al*, 1988; Hirsch & Barnes, 1994; Kane, 1994; Thompson, 1994). We know, however, that there are serious dose-related side-effects which make the use of high-dose treatment problematic in clinical practice. Likewise the concept of chlorpromazine equivalence is arbitrary, though necessary if the implementation of guidelines and the development of treatment protocols is to be possible. In the absence of previous studies studying high-dose treatment specifically, we have used our own definition of high-dosage.

The guidelines produced by the Royal College of Psychiatrists cover record keeping and actual clinical practice (Thompson, 1994). These will promote audit and further study on the risks relating to high-dose treatment. We have shown that the guidelines can be used in audit, although this inevitably involves subjective judgements about the quality of case notes. The importance of physical monitoring is, however, beyond dispute, as dangerous cardiac and haematological side-effects may be dose-related.

In our study, a large number of patients in a special care unit were treated with antipsychotic drugs in doses exceeding a chlorpromazine equivalent of 1000 mg, though this reduced after implementing the guidelines. A small, though important, minority was on doses exceeding *BNF* recommendations for a single drug. In the first sample, patients who were treated with high doses were more likely to have a diagnosis of schizophrenia. High dose patients were more likely to be subject to antipsychotic polypharmacy, but the use of more than one antipsychotic was frequently the result of transferring a patient from oral to depot drug administration and this could take several weeks.

The proportion of patients who were treated with doses exceeding the *BNF* recommended maximum was similar to previous surveys of prescribing in medium secure units (Gill, 1993; Stanley & Doyle, 1993). In the first sample, there was a higher proportion of female patients on high dose treatment than might be expected. Fraser & Hepple (1992) have commented on this previously but there seems to be no obvious

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explanation. They also noted that higher doses are used in forensic settings without a clear rationale. We found a low incidence of severe adverse reactions that required discontinuing a drug. This compares to the work of Pilowsky *et al* (1992) who, in a study of rapid tranquillisation, found that serious side-effects were rare, even with intravenous use of high-dose antipsychotics. Other studies, however, have recorded a high incidence of adverse effects during rapid tranquillisation (Bollini *et al*, 1984; Baldessarini *et al*, 1988).

The first study demonstrated failure to clearly record the onset, indication and outcome of high-dose treatment and to monitor the patient's physical status. The one life-threatening adverse event (neutropenia) highlighted the need for monitoring. Although both studies found that less than half of case notes recorded that alternative therapeutic options were being explored, a number of the patients in the high-dose treatment groups were also treated with benzodiazepines, mood stabilisers, electroconvulsive therapy or clozapine. The completion of the audit cycle showed improvements in clinical practice, particularly with respect to the onset of, indication for and outcome of high-dose treatment and in monitoring the patients' physical status.

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