

PAPERS AND ORIGINALS

Methodology of monitored release of a new preparation: buprenorphine

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Summary and conclusions

The analgesic agent Temgesic (buprenorphine) was made available under monitored release regulations for one year, which yielded data from 1736 doctors on 9123 patients. An analysis of 17 120 administrations of the drug confirmed the results of the pre-licensing clinical studies encompassing data from nine British hospitals on 483 patients.

No important new adverse effects attributable to the product were observed, and apart from giving reassurance, the usefulness of monitored release is questioned in the light of the relatively small amount of additional information arising from it.

Introduction

The controlled release of new products, particularly new chemicals, under monitored release regulations has been favoured by the Committee on Safety of Medicines to detect unwanted effects or adverse reactions when the incidence may be low. It has been assumed that such adverse effects may not appear in clinical trials conducted to secure registration but will become apparent in the much larger number of patients available for study after the drug's release into hospitals or general practice.

In 1977 the Licensing Authority granted a product licence for Temgesic (buprenorphine) for use in hospitals as a strong analgesic for patients with moderate and severe pain while undergoing terminal care for malignancy, postoperative pain,

and pain after myocardial infarction, but they stipulated that the release should be monitored. The application for the product licence was based on more than 500 intravenous and intramuscular administrations to patients after operation or with cancer who were in moderate to severe pain. In none of the 19 clinical trials in this country, which included comparisons with morphine and pentazocine, were serious adverse effects noted.

Methods

The responsibility for the drug and the costs of monitoring it in its first year of marketing were borne entirely by this pharmaceutical house. The system for monitoring was devised and set up by the company's medical, marketing, and statistical departments in consultation with the medical assessor at the medicines division of the Department of Health and Social Security and was subsequently controlled from within the medical department. The DHSS required a progress report at six-monthly intervals, but the total population to be studied was not defined. The company, therefore, set out to achieve a target of about 10 000 patients in about one year.

So that we obtained returns from the doctors as quickly as possible, we kept the monitoring simple and non-invasive. We asked doctors to record blood pressure, pulse, and respiratory rates before and two and four hours after each injection. The analgesic effect was recorded as poor, adequate, or good, and space was provided on the report forms for previous and concurrent medication, other effects, comments, and observations. The patient's sex, age, diagnosis, and operation, when relevant, were included, and each patient was given a unique number to ensure that confidentiality was maintained during data processing.

The report forms were designed with boxed answer spaces to simplify completion and to facilitate transcription to magnetic tape for computer analysis. Doctors filling in these forms had only to record their findings; they were not required to codify them (fig). Completed records were returned to the medical department by free post. Information about the monitored release was disseminated for the first six months by 11 specially trained hospital representatives. There was no advertising or mailing during this period, and the company elected to restrict supplies to only registered participants. The representatives approached anaesthetists, surgeons, and other consultants in teaching and major district hospitals to enlist their help but also visited hospital pharmacists, to whom materials would be sent, so that they were kept fully informed.

We sent 40 1-ml ampoules of Temgesic to the pharmacy for each

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consultant who agreed to co-operate, and further supplies were provided as necessary on request. No charge was made for the product during the first six months. After six months Temgesic was made commercially available to all hospitals and could be obtained in the normal way through the usual wholesale channels. The monitored release system was explained to all hospital prescribers, pharmacists, and relevant senior nursing staff by representatives, who left supplies of report forms for use by those expressing interest in the scheme.

As completing each form entailed extra work for the doctors we offered them a small fee, even though the monitoring was required by the Licensing Authority. A registration fee of £10 was available for each consultant agreeing to co-operate and a further £15 for every 10 fully completed record forms received by the company. Attitudes towards payment varied widely: some doctors simply refused to accept it, a few were angry that it was offered, while others complained that it was not enough for the work entailed.

All completed patient record forms were received by one trained secretary, who scrutinised them before passing them to the statistics department for processing. Any form with unusual findings or not fully completed was passed to one of us (AEW) for follow-up. Code numbers, not patient names, were used in the computer input forms, so that complete confidentiality was retained within the medical department. The data were input on to a file in an IBM 370/158 computer and were processed using the INQUIRE (Infodata Systems Inc) database management system. This provided online access, giving a rapid turnaround for specific inquiries from either doctors or the medical department. Full reports were produced at monthly intervals.

Results

In the first six months 970 doctors returned 5423 completed patient record cards. This represented 40% of the doctors who had agreed to co-operate in collecting data. The lag between distributing the initial supply of materials and record forms and receiving the forms at the monitored release unit was between one week and seven months.

TABLE I—Indication for strong analgesic

	Sex		Sex not reported	Total No (%)
	Male	Female		
Postoperative pain ..	2949	4564	35	7548 (82.7)
Pain from cancer ..	128	156	2	286 (3.1)
Chest pain ..	85	25		110 (1.2)
Renal pain ..	20	10		30 (0.3)
Preoperative analgesic ..	95	262		357 (3.9)
Peroperative analgesic ..	236	339	4	579 (6.3)
Miscellaneous ..	119	91	3	213 (2.3)
Total ..	3632	5447	44	9123

TABLE II—Results of analgesic injections after two and four hours reported during first six months and after full year of monitored release

	First injection				Subsequent injections			
	6 months		12 months		6 months		12 months	
	2 hours	4 hours	2 hours	4 hours	2 hours	4 hours	2 hours	4 hours
No for whom analgesic effect recorded ..	3830	3535	7705	7088	3415	3124	7095	6375
No (%) in whom analgesia adequate or good ..	3473 (90.7)	3094 (87.5)	7073 (91.8)	6313 (89.1)	3188 (93.4)	2727 (87.3)	6660 (93.9)	5636 (88.4)

TEMGESIC Monitored Release



STRICTLY CONFIDENTIAL

TEMGESIC INJECTION

Monitored Release Patient Record Card

CARD NO **Nº 107487** PATIENT NO BATCH NO
R R C Use only

Has a previous card been filled in for this patient? Yes No Please tick
 If Yes, please state number of previous card

Name of Doctor _____
 Hospital _____
 Address of Hospital _____
 Patient Identification (Name and/or Hospital No.) _____
 Age _____ Years Male Female
 Diagnosis or Operation _____
 Premedication (Specify Drug, Dose, Time) _____

1st or 4th INJECTION

Date Time _____ a.m./p.m.
 Dose (mg) _____ Route I M I V
Please tick

Clinical Observation	Before Injection	After 2 hours	After 4 hours
Respiration (Rate/min)			
Pulse (Rate/min)			
Blood Pressure			
Analgesia	Poor <input type="checkbox"/> Adequate <input type="checkbox"/>	Good <input type="checkbox"/> Poor <input type="checkbox"/>	Adequate <input type="checkbox"/> Good <input type="checkbox"/>
Other Drugs			
Other Effects			
Other Comments and Observations			

Other Drugs _____
 Other Effects _____
 Other Comments and Observations _____

2nd or 5th INJECTION

Date Time _____ a.m./p.m.
 Dose (mg) _____ Route I M I V
Please tick

Clinical Observation	Before Injection	After 2 hours	After 4 hours
Respiration (Rate/min)			
Pulse (Rate/min)			
Blood Pressure			
Analgesia	Poor <input type="checkbox"/> Adequate <input type="checkbox"/>	Good <input type="checkbox"/> Poor <input type="checkbox"/>	Adequate <input type="checkbox"/> Good <input type="checkbox"/>
Other Drugs			
Other Effects			
Other Comments and Observations			

Other Drugs _____
 Other Effects _____
 Other Comments and Observations _____

3rd or 6th INJECTION

Date Time _____ a.m./p.m.
 Dose (mg) _____ Route I M I V
Please tick

Clinical Observation	Before Injection	After 2 hours	After 4 hours
Respiration (Rate/min)			
Pulse (Rate/min)			
Blood Pressure			
Analgesia	Poor <input type="checkbox"/> Adequate <input type="checkbox"/>	Good <input type="checkbox"/> Poor <input type="checkbox"/>	Adequate <input type="checkbox"/> Good <input type="checkbox"/>
Other Drugs			
Other Effects			
Other Comments and Observations			

Other Drugs _____
 Other Effects _____
 Other Comments and Observations _____

Doctor's Signature _____ Date _____
R R C Use only
 Do you intend to use another record card for this patient? Yes No

The median number of patients per responding doctor was 12-15. In the second six months the number of doctors almost doubled to 1736 and the number of patient record cards rose to 12 353. Twenty-one doctors each sent in over 100 forms, accounting for over a quarter of the total number of forms returned.

The restrictions on the product licence were lifted in September 1978 after one year's monitored release to 9123 patients, but forms were still accepted until 31 December 1978, by which time reports had been received on 19 516 injections in 10 442 patients. By 15 September 1978 the records of 17 120 administrations in 9123 patients had been analysed. Patients ranged in age from 3 to 99 years; 3632 were male and 5447 female, while in 44 sex was not recorded. The doses most often prescribed were 0.3 mg (10 241 administrations) and 0.6 mg (4370 administrations). Table I shows the reasons for giving a strong analgesic.

Analgesic efficacy—Table II shows an assessment of analgesic effect after the first and subsequent administrations of the drug and was calculated from the six-month and 12-month figures. Information about the duration of action may be deduced from the intervals that elapsed between adjacent pairs of injections administered within a total time span of less than 36 hours. In 6881 injections given to patients requiring repeated analgesic the mode of the time interval between injections was 6.58 hours and the median 8.39 hours.

Event reporting—Doctors were asked to comment spontaneously on events as they were observed; specific adverse effects were not mentioned on the record form. Forty-four separate types of events were reported, although some probably overlapped and many may have been related to the patient's illness rather than the drug—for example, the incidence of nausea and vomiting was greater in patients with renal colic or myocardial infarction than in the total population studied (table III). The miscellaneous group of adverse effects included amnesia, bloating, cough, cramp, diarrhoea, diplopia, flatulence, and other subjective symptoms. Twenty-two patients (0.27%) were described as euphoric after the injection, of whom 17 were given the

drug postoperatively and nine were reported on by one surgeon. The euphoria was always transient and usually associated with relief from pain and preoperative anxiety. Hallucination was described in only seven patients (0.09%), but on follow-up it was confirmed that two patients had been hallucinating before treatment, one had a psychiatric history, and three were thought to be suffering from postoperative confusion rather than disordered perception. Retrospective follow-up in these cases provided all the necessary information.

TABLE III—Adverse effects and other recorded events

Adverse effect	No of patients	% of patients (n = 8187)
Nausea	722	8.8
Vomiting	603	7.4
Drowsiness	356	4.3
Sleeping	155	1.9
Dizziness	97	1.2
Sweating	80	0.98
Headache	45	0.55
Confusion	43	0.53
Lightheadedness	31	0.38
Blurred vision	23	0.28
Euphoria	22	0.27
Dry mouth	9	0.11
Depression	7	0.09
Hallucinations	7	0.09
Miscellaneous	318	3.9

Respiratory monitoring—Altogether, 9123 patients were monitored before and after injection to observe the effects of Temgesic on respiration and to assess the clinical importance of any changes. Of these patients, 936, to whom the drug was administered as premedication or during operation, were considered separately. Respiratory rates of less than 10/min, a convenient but purely arbitrary reference rate, were recorded in 96 of the remaining 8187 patients, but in most cases were noted without clinical comment and were probably not of practical importance. Information was volunteered on 42 patients (0.5%) who were given stimulants, reversal agents, or other forms of respiratory support. Some were given the drug during operation and others appear to have had depressed respiration before receiving Temgesic. There was no evidence of further respiratory embarrassment in 33 patients who were taking bronchodilator drugs.

Cardiovascular monitoring—Systolic and diastolic blood pressures and pulse rates changed in both directions, not a surprising finding in a group containing so many patients treated after operation. Bradycardia was not a feature of the drug treatment, pulse rates of less than 50/min being reported in 43 patients (0.53%) before injection and 39 (0.48%) afterwards. Tachycardias of more than 120/min were recorded in 111 patients (1.4%) before injection and 222 (2.7%) afterwards, but only 11 patients had both tachycardia and hypotension as defined by a systolic pressure of less than 100 mm Hg, of whom six (0.07%) were in a similar state before the drug was given. Buprenorphine had a useful

analgesic action in the 110 patients with chest pain, over 100 of whom had myocardial ischaemia or infarction.

Discussion

The company had collected details of 17 120 injections given to 9123 patients after a year's monitored release of buprenorphine. The results confirmed the profiles of both the analgesic and the adverse effects thereby increasing confidence in the product but adding little to the knowledge and understanding gained already from the preregistration clinical trials in 483 patients. Eighty per cent of those patients had experienced pain relief for at least four hours after an intramuscular injection of buprenorphine. A similar proportion of patients reported adequate or good relief four hours after injection during the monitored release. No clinically important changes in blood pressure occurred in either the preregistration trials or the monitored release. In both studies statistically significant falls in respiratory rates were recorded but in neither case were they of practical importance.

The adverse effect profiles in the two studies were similar, and no new adverse effects attributable to the product were brought to light. If an adverse effect had not occurred in the 483 patients studied in the preregistration trials we could be 95% certain that the "true" incidence was less than 0.8%. The chance of detecting less common effects may be improved by increasing the cohort size. Absence of an adverse effect in 1000 cases, for example, allows us to conclude with 95% confidence that the true incidence is less than 0.4%, and a negative finding in 9000 cases allows us to be sure, with the same degree of confidence, that the incidence is less than 0.04%. A major problem arises if an adverse effect occurs in a large cohort. How do we decide whether there is a causal relation with whatever drug has been administered? Control cohorts become necessary and practical difficulties then ensue. Monitored release, however large the cohort size, without a suitable (randomised?) control group is, therefore, a methodological impasse when rare effects are considered.

On the positive side, therefore, monitored release enables a wealth of data on the use of the product in routine clinical practice to be collected and stored. On the negative side, the cost in time to those participating in the scheme, and in time and money to the company, must be considered and, inevitably, will add to the cost of developing a new drug.

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ONE HUNDRED YEARS AGO Drs Dujardin-Beaumont and Audige have recently published a work, setting forth the result of their experimental researches on the toxic power of the various alcohols. This volume is chiefly composed of the diary of nearly three hundred experiments, which the authors have carried out with perseverance and method, which give to their researches every possible scientific value. The object which they proposed to themselves from the outset has been, not to compare the action of alcohol on animals with its action upon man, but to compare the effects in the same animal series of the various alcohols. Every one knows that modern chemistry, greatly aided by the researches of M Wirtz and M Berthelot, has succeeded in isolating the products of fermentation, and in obtaining, by distillation or by synthetic constitution, bodies which, by their composition and by their properties and by their action on the organism, differ more or less from methyl alcohol, or the alcohol of wine, which is the type of alcohols. It is known, moreover, that these bodies have been divided into monatomic or polyatomic, according as their atomic combinations are more or less complex. The experiments of Dr Dujardin-Beaumont and Dr Audige have related to these various compounds, either alone or combined in a variable proportion; only wishing to occupy themselves with acute alcoholic poisoning, they have taken, as the limits of toxic doses, the quantities of pure alcohols which, in proportion to the weight of the animals, are necessary to cause death in the space of from twenty-four to thirty hours, with gradual and persistent lowering of the temperature; and it results,

from their numerous experiments, that the toxic power of the alcohols is so much more energetic in proportion as their atomic constitution is the more complex. Now, that which constitutes the chief interest of these researches is that the majority of these alcohols—propylic, butylic, amylic, oenanthic, caprylic, etc.—enter in variable proportions into the composition of the alcohols sold under the name of brandy in the cheap trade in drinks. Having now ascertained the toxic effects of the various alcohols on which they have experimented, in an isolated form and in a state of purity, they are about to undertake a new series of researches, with the object of studying on the guinea-pig the effects of chronic alcoholism, employing exclusively those spirits which are daily sold in the cheapest drink-shops. The interest from the point of view of public health on such researches does not need to be insisted on. Already, M Bergeron, who reports on these researches, had laid before the Academy his grounds for believing that the impurity of the beet-root spirit, grain spirit, and potato spirit, which at present have largely replaced the alcohol of wine in consumption of spirits, is responsible for the violent and brutal forms of modern drunkenness, and the gravity of the alcoholism observed in our days. M Michel Levy, as well as Messrs Fauvel and Bouchardat, share those opinions, and concur in conclusions which aim at restraining the production of these commercial alcohols as dangerous to the moral and physical hygiene of the population. (*British Medical Journal*, 1879.)