Information in practice

Computer support for determining drug dose: systematic review and meta-analysis

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Abstract

Objective To review the effectiveness of computer support for determining optimum drug dose.
Design Systematic review of comparative studies where computers gave advice to clinicians on the most appropriate drug dose. Search methods used were standard for the Cochrane Collaboration on Effective Professional Practice.
Subjects Comparative studies conducted worldwide and published between 1966 and 1996.
Main outcome measures For qualitative review, relative percentage differences were calculated to compare effects of computer support in different settings. For quantitative data, effect sizes were calculated and combined in meta-analyses.
Results Eighteen studies met the inclusion criteria. The drugs studied were theophylline, warfarin, heparin, aminoglycosides, nitroprusside, lignocaine, oxytocin, fentanyl, and midazolam. The computer programs used individualised pharmacokinetic models to calculate the most appropriate dose. Meta-analysis of data from 671 patients showed higher blood concentrations of drug with computer support (effect size 0.69, 95% confidence interval 0.36 to 1.02) and reduced time to achieve therapeutic control (0.44, 0.17 to 0.71). The total dose of drug used was unchanged, and there were fewer unwanted effects of treatment. Five of six studies measuring outcomes of care showed benefit from computer assistance.
Conclusions This review suggests that using computers to determine the correct dose of certain drugs in acute hospital settings is beneficial. Computers may give doctors the confidence to use higher doses when necessary, adjusting the drug dose more accurately to individual patients. Further research is necessary to evaluate the benefits in general use.

Introduction

Maintaining therapeutic drug concentrations is a complex task requiring knowledge of medicine and pharmacokinetics, a good rapport with the patients, and some skill in calculating dose. Harm can be caused by miscalculating doses because many drugs have a narrow "window" in which therapeutic benefits can be obtained at a low risk of unwanted effects.

Monitoring drug treatment to optimise effects and minimise dangers can be time consuming and requires meticulous attention to detail. Doctors sometimes make errors of judgment because their capacity to process information is exceeded,[1] and their computational skills may be inadequate to perform calculations about drug dose.[2] For example, 82 of 150 hospital doctors were unable to calculate how many milligrams of lignocaine were in a 10 ml ampoule of 1% solution.[3]

Computers, however, are very good at gathering information and performing repetitive calculations. Several computer systems have been designed to help doctors to determine the optimum dose of drugs. We assessed the benefits of these systems to establish whether they should be used more widely.

Methods

Inclusion criteria

We identified all comparative studies in which computers were used to help determine the most appropriate drug dose. The criteria for entry into the review were standard for reviews undertaken by the Cochrane Collaboration on Effective Professional Practice and include methodological and quality criteria for rigorous design of experimental and quasi-experimental studies.[4]

Methodological criteria were

- Studies using any objective measure of patient outcome or provider behaviour, randomised or quasi-randomised by patient, doctor, practice, or provider of health care
- Interrupted time series with a clearly defined intervention and at least three time points before and three after the intervention
- Non-randomised studies controlled at a second site with data before and after the intervention and appropriate choice of control site.

We included all studies using a reliable, objective, predetermined measure of the process or outcome of health care. This includes studies comparing computer aided decisions either to unassisted decisions or to decisions made using aids such as nomograms, as well as studies in which the computer directly administered the drug to patients (such as with a computer controlled pump). We excluded studies in which the computer simply suggested giving or withholding a drug. The criteria were applied independently by two researchers

and any disagreements were resolved by group discussion.

Search strategy

Relevant studies were located from the specialised register of studies of the Cochrane Collaboration on Effective Professional Practice.[5] This register is updated by electronic searches and hand searches of relevant journals. We also located references through bibliographies of related topics and contact with experts and pharmaceutical companies. We made specific searches of Medline and Embase from 1966 to June 1996 to identify relevant references. The search terms were "computer assisted decision making" *or* (prescr* *and* comput*) *and* ("randomised controlled trial" *or* "random allocation" *or* "double blind method"). Search strategies were modifications of those designed to give a high yield of randomised controlled clinical trials.[6] In addition, we hand searched issues of *Therapeutic Drug Monitoring* published from January 1993 to July 1996.

Outcomes

Outcome measures, determined in advance, were

- Proportion of patients in which drug dose is changed because of computer advice
- Proportion of patients with unwanted effects of treatment
- Proportion of patients with blood concentrations of drug or a physiological measurement within the desired range
- Differences in blood concentrations of drug or physiological measurements attributable to computer support
- Time to achieve therapeutic control
- Proportion of patients with improved outcome attributable to computer advice.

To these we subsequently added changes in the cost of treatment attributable to computer support.

Data extraction

Two researchers reviewed each study independently and, using a standard form, extracted data on methodology, outcomes, and quality criteria.[4] We recorded the unit of allocation and analysis, concealment of allocation, blinding, statistical power, follow up of patients and professionals, baseline measurements, and protection of the control group from contamination by the intervention. We calculated the mean difference in outcome with computer support, as a percentage of the mean value without support for all outcomes fitting our criteria for inclusion. These relative percentage differences were used in the narrative part of the review.

Quantitative analysis

Studies with comparable outcomes were divided into groups for meta-analysis according to outcome measure. Of the six predefined outcome measures, only four provided suitable data for meta-analysis: dose of drug; blood concentrations of drug; time to reach therapeutic concentration or effect; and difference between patients' drug concentration and target concentration. Four separate meta-analyses were performed.

We estimated effect sizes as standardised weighted mean differences for each outcome in each study where the relevant data were available. The effect size is a statistical measure of the impact of the intervention that is independent of the units used to measure an outcome. This measure quantifies the effect of an intervention in units of standard deviation and allows comparison of studies of the same intervention that measured different outcomes.

We used a random effects model to combine the effect sizes to give an overall effect for each subgroup of studies. This model was chosen because the outcomes we combined were for studies on different drugs and different diseases. The random effects model allows quantitative combination of outcomes but does not assume that all interventions have the same underlying effect. If the outcome was measured at different times in the same study, we selected the value nearest the midpoint of the intervention period. When there were related outcomes from the same study we used the mean of the effect sizes.[7] In this way only a single effect size for each study was pooled. We performed calculations using the RevMan software provided by the Cochrane Collaboration.

Results

Characteristics of included studies

We identified 23 relevant studies, of which 16 randomised controlled clinical trials[8–23] and one non-randomised controlled clinical trial[24] met the inclusion criteria. All used reliable outcome measures with adequate blinding of assessment. No interrupted time series or studies controlled at a second site were identified. Sixteen studies used patients as the unit of allocation; one allocated medical firms to intervention and control.[9] Three studies did not use the same unit for allocation and analysis.[9 12 16] Only two studies reported a power calculation.[11 15] Six studies reported adequate concealment of allocation (for example, random numbers in opaque envelopes),[8–13] 12 followed up more than 80% of patients,[8 12 13 15–20 22 24 25] 12 reported similar baseline measures between intervention and control groups,[8–14 16 19 20 23 24] nine recorded that patient consent had been obtained,[8–10 15 18–20 22 23] and eight reported gaining approval from an ethics committee.[8 10 12 18–20 22 24] In one study the reviewers thought that there was little room for improvement because the performance of the health professional was adequate without the intervention.[23]

Most studies were randomised by patient, so the same health professional might have given treatment to study and control groups. If the same person treated both groups it is possible that the effect of computer advice might have carried over into the control group. Such studies would tend to underestimate the effect of computer support. Two studies of continuous infusion anaesthesia, although randomised by patient, had a sufficiently rigorous study design to ensure that this contamination was unlikely to occur.[19 24] In these studies a computer controlled pump delivered the drug directly to the patient, and the anaesthetist administered additional anaesthetic agents without knowing the amount of drug given by the computer. In the study randomised by medical firm all firms worked at the same hospital, so the computer advice might have

influenced treatment of the control group. The only studies judged to be free of contamination were the two studies of continuous infusion anaesthesia.

Types of computer support systems used

Most of the computer systems used a mathematical model of the pharmacokinetics of the drug in question to predict the required dose (table). These models represent the compartments in the body in which the drug is distributed. Rate constants are used to describe the movements of the drug between different compartments. The models ranged from a simple, one compartment model for theophylline[14] to a more complex, three compartment model for fentanyl.[24] The starting values for the rate constants were estimated from population data but could then be adjusted as data accumulated from an individual patient. The systems allowed the operator to specify a target blood concentration of drug, which the computer then attempted to achieve. When the effect of the drug was more important than its blood concentration, pharmacodynamic parameters based on population data were added to the model.[22]

Effects of computer support on outcome

The table shows the effects of computer support on the process and outcome of care.

Drug doses used—Eleven studies examined change in the drug dose when computer support was used,[8 9 11 13 14 17–19 21 23 24] and seven found significant changes.[8 13 14 17 19 21 24] Studies on theophylline showed increases in initial dose[14 21] and in maintenance dose.[13 14] Studies on intravenous anaesthesia showed a reduction in total dose of fentanyl used[24] and a reduction in initial dose and maintenance dose of midazolam.[19]

Effects of computer support on the process and outcome of care (ordered by clinical problem)

Study	Intervention *v* control	Relative percentage differences between effects of intervention and control (mean intervention value *v* control value)	P value of difference
Treating acute asthma with theophylline			
Casner 1993, USA[10]	Advice based on linear one compartment model (n=17) *v* usual care (n=18)	Blood concentration of drug increased 19% (15 *v* 12.6 μg/ml)	>0.05
		Time for infusion increased 28.1% (4.1 *v* 3.2 days)	>0.05
		Hospital stay increased 29.5% (11.4 *v* 8.8 days)	>0.05
Gonzalez 1989, USA[13]	Advice based on bayesian one compartment pharmacokinetic model (n=37) *v* population based guidelines (n=30)	Initial dose increased 10.5% (4.2 *v* 3.8 mg/kg)	0.5
		Maintenance dose increased 50% (0.6 *v* 0.4 mg/kg/hour)	0.0001
		Blood concentration of drug increased 19.7% (14.6 *v* 12.2 mg/l)	<0.002
		Percentage of patients in therapeutic range at 4 hours increased 28.1% (14.6% *v* 11.4%)	NA
		Percentage of patients discharged home increased 10.6% (52% *v* 47%)	>0.05
Hurley 1986, Australia[14]	Estimate of theophylline clearance based on one compartment linear pharmacokinetic model (n=48) *v* usual care based on theophylline blood concentrations (n=43)	Initial dose increased 10% (250 *v* 227 mg)	<0.01
		Maintenance dose increased 133% (831 *v* 698 mg/day)	0.0023
		Serum concentration of drug reduced 10.1% (16.1 *v* 17.9 μg/ml)	>0.05
		Time for infusion increased 1.4% (22.4 *v* 22.1 hours)	<0.05
		Percentage of patients with toxic drug concentrations reduced 50% (18.9% *v* 37.8%)	0.04
		Hospital stay reduced 28% (6.3 *v* 8.7 days)	0.027
		No of deaths reduced (0 *v* 2)	>0.05
Verner 1992, Israel[21]	Dose advice based on individualised pharmacokinetic model (n=10) *v* usual care (n=15)	Initial dose increased 162% (437 *v* 167 mg)	NA
		Blood concentration of drug increased 6% (13.8 *v* 13.0 μg/ml)	<0.05
		Percentage of time within therapeutic range increased 51% (77% *v* 51%)	>0.05
		Clinical improvement score increased 6% (5.3 *v* 5.0)	>0.05
		Hospital stay unchanged (4 days)	NA
Anaesthesia for cardiac surgery with fentanyl			
Alvis 1985, USA[24]	Computer controlled pump using three compartment open model (n=10) *v* manual administration (n=10)	Intervention 1 (computer maintained stable serum drug concentration):	
		Total dose reduced 38% (19.6 *v* 27.1 μg/kg)	<0.05
		No of hypotensive episodes reduced 20% (4 *v* 5)	>0.05
		Need for additional anaesthetics increased 14% (8 *v* 7 events)	>0.05
		Intervention 2 (computer allowed manual adjustment of serum concentration):	
		Total drug dose reduced 16.3% (19.6 *v* 22.8 μg/kg)	>0.05
		No of hypotensive episodes reduced 60% (2 *v* 5)	<0.05
		Need for additional anaesthetics reduced 43% (4 *v* 7 events)	<0.05
Anaesthesia for cardiac surgery with fentanyl and midazolam			
Theil 1993, USA[19]	Computer controlled pump using pharmacokinetic model to achieve target serum concentration (n=12) *v* infusion controlled by doctor (n=12)	Midazolam:	
		Initial dose reduced 43% (0.08 *v* 0.14 μg/kg)	<0.05
		Maintenance dose reduced 33% (0.4 *v* 0.6 μg/kg)	<0.05
		Plasma concentration reduced 47.9% (50 *v* 96 ng/ml)	<0.05
		Fentanyl:	
		Initial dose increased 25.1% (6.52 *v* 5.21 μg/kg)	>0.05
		Maintenance dose unchanged (0.08 μg/kg)	NA
		Total dose increased 14.3% (34.61 *v* 30.27 μg/kg)	>0.05
		No of additional drug interventions reduced 8.6% (64 *v* 70)	>0.05
Anticoagulation with heparin			
Mungall 1994, USA[15]	Starting doses generated by bayesian model *v* doctors using nomogram (total n=51)	Drug dose increased 8.4% (1290 *v* 1190 units)	>0.05
		Percentage of patients with APTT ratio >1.5 in first day increased 21% (94% *v* 78%)	0.009
		No of blood tests reduced 18% (2.3 *v* 2.8 tests/person/day)	<0.05
		No of adverse events reduced (0 *v* 24)	<0.05

continued on page 987

Continued from p 986

Study	Intervention v control	Relative percentage differences between effects of intervention and control (mean intervention value *v* control value)	P value of difference
Anticoagulation with warfarin			
Fihn 1994, USA[12]	Follow up times suggested by mathematical model (n=301) *v* usual care (n=319)	Scheduled follow up interval increased 25% (4.4 *v* 3.5 weeks)	<0.05
		Actual follow up interval increased 7% (4.4 *v* 4.1 weeks)	<0.05
		No of bleeds reduced 19% (5.4 *v* 6.7 events/100 patient years)	>0.05
		No of embolisms increased 71% (2.4 *v* 1.4 events/100 patient years)	NA
Poller 1993, UK[16]	Computer advice on dose (intervention 1 n=57, intervention 2 n=53, intervention 3 n=12) *v* usual care (n=64)	Proportion of tests in therapeutic range increased 12%, 5%, and 11% respectively (intervention 1 57%, intervention 2 53%, intervention 3 56%, control 50%)	>0.05 for all interventions
White 1987, USA[22]	Initial dose suggested by bayesian pharmacokinetic and pharmacodynamic model (n=39) *v* usual care (n=36)	No of patients with blood concentration above therapeutic level reduced 70% (5% *v* 17%)	0.11
		Time to reach stable dose reduced 39% (5.4 *v* 6.7 days)	0.002
		Time that blood concentration remained at therapeutic level increased 16% (58 *v* 42 days)	0.001
		Hospital stay reduced by 35% (13 *v* 20 days)	0.01
		Percentage of patients with bleeding complications reduced (0 *v* 8.3%)	0.05
White 1991, USA[23]	Maintenance dose suggested by bayesian pharmacokinetic model (n=24) *v* usual care (n=25)	Percentage of patients requiring change in dose increased 5% (20% *v* 15%)	>0.05
		Percentage of patients with prothrombin time in target range reduced 14% (43% *v* 50%)	>0.05
		Time to next visit increased 6.9% (18.7 *v* 17.5 days)	>0.05
Control of ventricular arrhythmia with lignocaine			
Rodman 1984, USA[17]	Initial dose suggested by individualised linear two compartment pharmacokinetic model (n=9) *v* usual care (n=11)	Dose increased 76.2% (3.7 *v* 2.1 μg/ml)	<0.01
		Infusion rate in first hour increased 96% (83 *v* 43 mg/kg/min)	<0.01
		Percentage of patients with blood concentration in therapeutic range increased 70% (89% *v* 64%)	0.44
Induction of labour with oxytocin			
Willcourt 1994, USA[8]	Computer controlled pump with "closed loop" feedback on uterine activity (n=114) *v* nurse controlled continuous infusion (n=196)	Dose reduced 641% (1.1 *v* 8.15 mU/min) but computer controlled pump delivered pulsatile oxytocin	0.006
		Duration of infusion reduced 12% (366 *v* 417 min)	0.35
		Cord lactate concentration reduced 11% (3.35 *v* 3.75 mmol/l)	0.032
		Percentage of patients needing caesarean section reduced 15% (11.5% *v* 13.5%)	0.037
Treating infection with aminoglycosides			
Burton 1991, USA[9]	Advice based on bayesian pharmacokinetic model (n=72) *v* usual care (n=75)	Initial dose increased 3.5% (238 *v* 230 mg/day)	>0.05
		No of patients with peak concentration in therapeutic range increased 37.5% (82.9% *v* 60.3%)	>0.05
		No of patients with trough concentration in therapeutic range increased 7.0% (91.3 *v* 85.3)	>0.05
		Hospital stay reduced 26% (13 *v* 17.6 days)	0.013
		Percentage of patients with clinical response increased 9.0% (88.2% *v* 80.9%)	>0.05
Destache 1990, USA[11]	Patients whose doctors accepted advice based on one compartment bayesian pharmacokinetic model (n=75) *v* those of doctors who did not (n=70)	No of dose changes increased 78.1% (0.64 *v* 1.14)	<0.005
		Percentage of patients with adequate trough concentrations increased 127% (25% *v* 11%)	<0.05
		Duration of treatment increased 0.8% (109.81 *v* 108.95 hours)	>0.05
		Time taken to reduce elevated temperature reduced 45% (50 *v* 92 hours)	<0.05
		Percentage of patients with nephrotoxicity reduced 44% (8.0% *v* 14.4%)	>0.05
		No of drug tests increased 6.8% (3.28 *v* 3.07)	NA
		Hospital stay reduced 27.4% (13.4 *v* 18.5 days)	>0.05
Postoperative analgesia with fentanyl			
Van den Nieuwenhuyzen 1995, Holland[20]	Computer controlled pump using pharmacokinetic model to achieve target drug serum concentration (n=9) *v* patient controlled morphine pump (n=10)	Time taken to onset of analgesia reduced 60% (20 *v* 50 min)	<0.05
		Time with pain score >3 units reduced 43% (12% *v* 21%)	<0.05
		No of demands for additional analgesia reduced 38% (21 *v* 43)	<0.05
Postoperative control of blood pressure with nitroprusside			
Ruiz 1993, Spain[18]	Fuzzy logic controlled pump with arterial pressure sensor (n=40) *v* usual care (n=20)	Infusion rate at one hour increased 36.6% (5.6 *v* 4.1 μg/kg/min)	>0.05
		Time that blood pressure in target range increased 23% (80% *v* 65%)	<0.001
		Difference in mean arterial pressure reduced 57% (6.3 *v* 14.7 mm Hg)	<0.001

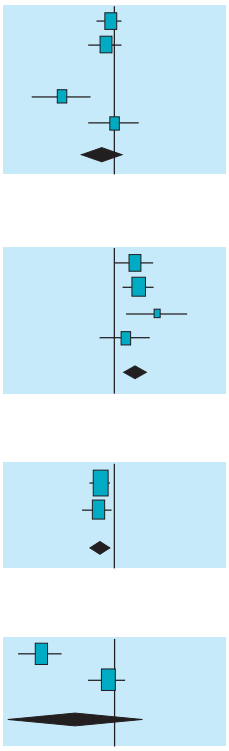
NA=Not available. APTT=Activated partial thromboplastin time.

Drug concentrations within desired range—Of the seven studies that measured changes in drug concentrations in the body two found significant increases in the proportion of patients with drug concentrations in the therapeutic range with computer support.[9-11 13 14 17 21]

Physiological control—Eight studies measured changes in control of a physiological parameter with computer support,[8 15 16 18 20 22–24] of which six showed significant benefit.[8 15 18 20 22 24] Computer support for anticoagulant control resulted in significant reductions in the time taken to achieve the desired prothrombin time[22] and activated partial thromboplastin time.[15] In postoperative control of blood pressure with sodium nitroprusside, a computer assisted pump was more effective at keeping blood pressure in the target range than a manually controlled infusion. Babies delivered to women treated with computer controlled oxytocin had a lower lactate concentration in the umbilical cord blood.[8]

Unwanted effects of drug treatment—Six studies measured the unwanted effects of drugs,[11 12 14 15 22 24] and four found significant reductions associated with computer support.[14 15 22 24] Fewer patients treated with theophylline reached toxic drug concentrations when computer advice was used.[14] In studies on anticoagulation both the number of patients given too much anticoagulant[22] and the total number of adverse events[15] were reduced in the intervention groups. The number of hypotensive episodes during cardiac surgery was

Study	Computer support: No of patients	Computer support: Mean value (SD)	Control: No of patients	Control: Mean value (SD)	Standardised mean difference (95% CI)	Weight (%)	Standardised mean difference (95% CI)
Drug dose							
Hurley[14]	48	0.78 (0.21)	43	0.80 (0.15)		31.9	−0.108 (−0.520 to 0.304)
Mungall[15]	25	1500 (430)	26	1600 (260)		28.2	−0.278 (−0.830 to 0.273)
Thiel[19]:							
Midazolam	12	0.40 (0.02)	12	0.60 (0.16)		18.5	−1.694 (−2.650 to 0.737)
Fentanyl	11	0.08 (0.02)	12	0.08 (0.02)		21.4	0 (−0.818 to 0.818)
Total (95% CI)	96		93			100	−0.426 (−0.998 to 0.146)
χ^2 = 9.51 (df=3) Z=1.46							
Blood concentration of drug							
Casner[10]	17	14.80 (3.00)	30	12.60 (3.80)		29.1	0.612 (0.003 to 1.221)
Gonzalez[13]	37	14.80 (2.70)	30	12.40 (3.80)		43.4	0.733 (0.235 to 1.231)
Rodman[17]	9	5.30 (0.90)	11	3.70 (1.33)		10.9	1.322 (0.330 to 2.315)
Verner[21]	10	18.10 (2.38)	15	17.30 (2.64)		16.6	0.304 (−0.501 to 1.110)
Total (95% CI)	73		86			100	0.691 (0.363 to 1.019)
χ^2 = 2.53 (df=3) Z=4.13							
Time to achieve therapeutic control							
Destache[11]	75	200.00 (79.38)	70	242.18 (122.50)		66.1	−0.409 (−0.739 to −0.080)
White[22]	39	7.00 (1.60)	36	8.30 (3.40)		33.9	−0.491 (−0.951 to −0.031)
Total (95% CI)	114		106			100	−0.437 (−0.705 to −0.169)
χ^2 = 0.08 (df=1) Z=3.20							
Difference from target therapeutic level							
Ruiz[18]	40	120.00 (3.10)	20	128.40 (4.50)		49.6	−2.291 (−2.975 to −1.607)
White[23]	23	1.00 (1.37)	24	1.30 (2.20)		50.4	−0.160 (−0.733 to 0.413)
Total (95% CI)	63		44			100	−1.217 (−3.305 to 0.871)
χ^2 = 21.91 (df=1) Z=1.14							



Quantitative effects of computer support for determining drug dose on outcomes of care (standardised weighted mean differences (95% confidence intervals) for computer support versus control)

reduced when fentanyl and midazolam were given via a computer controlled pump.[24]

Cost of drug treatment—Only two studies reported economic data, and both looked at computer support for aminoglycoside dose.[9 11] In one study the mean direct cost of treatment with computer support was $7102 compared with $13 758 in controls ($P < 0.02$), with a benefit to cost ratio of 75.[11] The other calculated a cost avoidance (the money potentially saved by the intervention) of $1311 for each patient treated, with a benefit to cost ratio of 4.1.[9] These cost savings resulted largely from reduced hospital stays, which was confirmed in one study,[14] although another suggested an increased time spent in hospital.[10] Another study showed that computer support lengthened the interval between outpatient visits.[12]

Outcome of medical care—Six studies directly measured outcomes of care, of which five showed benefits. Three showed significant benefits in clinical improvement scores for asthma,[21] treating infection,[9] and pain relief after surgery.[20] Fewer caesarean sections were required when oxytocin was given by computer controlled pump to augment labour.[9] With computer support for hospital treatment of acute asthma, fewer patients subsequently needed convalescent care,[13] and there were fewer deaths.[14] One study on anticoagulation showed an increase in the number of embolisms, but it may be that the computer system used in this study was set to achieve too low a prothrombin time.[12]

Overall effect—Eleven studies provided outcomes for quantitative synthesis,[10 11 13–15 17–19 21–23] and the figure shows the individual results and meta-analysis for each of the four outcome measures. Patients treated with computer support had higher blood concentrations of the drug (effect size 0.69, 95% confidence interval 0.36 to 1.02) and took less time to reach therapeutic concentrations (−0.44, −0.71 to 0.17). However, computer support had no significant effect on the total amount of drug used (−0.43, −1.00 to 0.15) nor on the difference between the level of a physiological parameter achieved and the target level (−1.22, −3.31 to 0.87). Although the clinical settings of the trials varied widely, only in the case of difference from target level was there evidence of statistical heterogeneity.

Discussion

This review suggests that substantial benefit results from computer support for determining the dose of certain drugs in acute hospital settings. In the studies we identified, unaided doctors were often excessively cautious in estimating drug dose. This caution presumably resulted from an unwillingness to expose patients to adverse effects of drug treatment. Unaided doctors used lower initial doses and maintenance doses than when computer support was available.[14 21] Lower doses lead to lower blood concentrations and often to suboptimal therapeutic effects. Although doses with computer support tended to be higher than those used by unaided doctors, no studies reported an increase in unwanted effects due to overdose. This suggests that the computers helped doctors to tailor drug doses

more accurately to individual patients. Higher initial doses with computer support gave more rapid therapeutic control,[20 22] bringing benefits for patients and reducing the time that they spent in hospital.[9 14 22] Unaided doctors tended to exercise caution in checking blood concentrations, which resulted in more blood tests[15] and hospital visits.[12]

The most successful systems were those in which the computer administered drugs directly to patients under medical supervision. Manually controlled infusions resulted in higher doses of anaesthetic agents compared with computer controlled infusions.[19 24] This may result from the doctors' reluctance to expose patients to the risk of unnecessary pain. However, patients treated with computer support experienced less pain,[20] suggesting that computer support could help doctors to adjust drug doses more accurately for individual patients.

Key messages

- This systematic review of studies examining computer support for determining optimum drug dose showed benefits from computer use
- Computer support led to patients having increased blood concentrations of drug, reduced time to achieve therapeutic benefits, and fewer unwanted effects of treatment
- Computer support helps doctors to tailor drug doses more closely to the needs of individual patients
- All the studies took place in hospitals, and further research is needed to determine the risks and benefits of widespread use of computer support, particularly in general practice, where most prescribing takes place

Methodological issues

Potentially, the most important factor that may undermine our analysis is publication bias—studies with positive results are more likely to be published than those with negative results.[26] Our search was exhaustive, and it seems unlikely that large numbers of patients have been randomised to trials that we have not identified. Orwin's file drawer method suggests that there would need to be 24 unpublished studies showing no benefit from computer support to alter our results significantly.[27]

Another review in a similar area did not use statistical methods to estimate the overall effects from computer support,[28] preferring to present a "vote count" of statistically significant studies. This method risks concluding falsely that an important effect is absent because it assumes that a trial with no significant effect is a negative study.[29] The method also does not make full use of available data. Our overview represents an advance from this approach, using established and robust statistical methods to estimate an overall treatment effect.[29 30]

Our findings need to be read with caution since we identified relatively few studies on a limited range of drugs and our quantitative analysis was based on results derived from only 671 patients. Computer assisted determination of drug dose is a potentially hazardous intervention: it is surprising that the risks and benefits have not been evaluated in large randomised controlled trials. The quality of the studies could be improved: most did not report a power calculation, and sample sizes were often small. A common bias in many of the studies was that the same clinicians treated patients allocated to intervention and control, so the effect of the intervention would tend to spill over into the control group. Contamination of the control group in this manner would tend to make it more difficult to show a benefit from computer support.

More large scale studies are needed to confirm our conclusions, and research is needed to examine the effects of computer support in general use and to develop and implement appropriate systems. Existing studies suggest that computer support for drug dosage will be cost effective, but economic evaluation should be an integral part of any future study. Economic benefits seen in one therapeutic area may not transfer to another clinical situation.

Implications for computer support for drug dose

The scope of computer support systems could be widened to include other, commonly prescribed drugs with a narrow therapeutic window, such as anticonvulsants and lithium. A computer might use the same basic pharmacokinetic model for several different drugs. It is possible that the model could be extended to predict the likelihood and severity of some interactions—for example, those caused by competition for protein binding sites.

A barrier to adopting computer support may be the lack of access to suitable computers and electronic medical records. Computerised records are used in some hospital departments (such as intensive care), but hospitals often rely on paper to record outpatient treatment. In contrast, most general practitioners routinely use electronic records for prescribing[31] and have easy access to suitable hardware that could run programs to help them to determine the most appropriate dose of commonly used drugs. General practice computers often already store necessary data such as blood concentrations of drugs, body mass index, and indicators of hepatic and renal function. It may be that the benefits seen in secondary care could be realised on a large scale if programs giving support for drug dose were integrated with the software routinely used in general practice.

A parallel version of this review will appear in the *Cochrane Library*. We thank referees in the Cochrane Collaboration on Effective Professional Practice review group for helpful comments on the protocol for this review. Since this review was conducted, the Cochrane Collaboration on Effective Professional Practice has changed its name to the Cochrane Effective Practice and Organisation of Care Group (EPOC).

Contributors: All the authors contributed to writing the protocol and participated in dual, independent data extraction and in reviewing drafts of the paper. RW developed the hypothesis, initiated the study, coordinated the review process, and wrote the original draft of the paper. RW and NF conducted the meta-analyses with advice from Frederick Wolf. SD constructed the data tables and hand searched *Therapeutic Drug Monitoring*. Emma Harvey helped to refine the protocol and contributed extensively to revising the paper. Andy Oxman helped to refine the study question. Martin Vessey, Pat Yudkin, and Mike Murphy commented on earlier drafts of the paper. RW is guarantor for the article.

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Correction

Information in practice: NHSnet—learning from academia

An authors' error occurred in this article by T J Roscoe and M Wells (6 February, pp 377-9). In the table (top of p 378) the first row actually showed the total annual budget of the tertiary education sector and of the NHS (not, as stated, the budget of their computer networks, JANET and NHSnet).

A mistake that changed my practice

The wrong notes

Our first visit to the antenatal clinic was an example of the poor quality service that you hear people complain about frequently in their dealings with the NHS: a 45 minute wait to be seen; being told by the antenatal receptionist to go to the ultrasound reception desk and vice versa. My wife went to the lavatory after the scan and was then asked for a sample of urine; we saw three members of staff who did not wear badges, did not introduce themselves, or ignored me as the father to be.

I wrote a letter of complaint in which I made suggestions on each point that would cost no money to implement but required something that money cannot buy—namely, staff modifying their working practices.

Our second visit was not much better and clearly little had changed. It wasn't until we got home and looked in our patient held maternity records that we realised that the results of another patient had been taken from the clinic notes and stuck in my wife's records. Presumably that day's entry had also been written in the wrong set of hospital notes. Different first name, different date of birth, different address. They got the surname right.

I thought about my own practice. People move house, and with the growing number of telecom providers, change their telephone number. I started asking parents to confirm their address and telephone number at the start of every consultation. Out of 100 consecutive consultations, there were 14 different telephone numbers and eight different addresses from those recorded in the notes. The numbers may have been higher among the non-attenders, which may explain their absence in some cases. Twice I was about to start writing in notes of patients with the same surnames but different first names. The surnames were right, but they were the wrong notes.

As the only letter from the consultation I write is to the parents, with copies to other relevant parties, it ensures that the parents get the letter I have promised, get the next appointment letter from me or others, and if I need to ring them I do not have the hassle of directory inquiries, ex-directory numbers, and ringing the general practitioner for the number. It takes 30 seconds at the start of the consultation to confirm these details and it can save a lot of time and embarrassment later. A simple quality measure that costs nothing.

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