model has facilitated rather than hindered the introduction of expensive drugs in our hospital. Other measures (the formulary, generic prescribing, purchase contracts, appropriate management practices, drug utilisation review programme) continue to be aggressively pursued to ensure the best value for money. These were not enough, however, to accommodate all requests for new drugs. We concede that the

model has not been formally validated, but it is being used successfully in several other Australian hospitals. The legal implications are real ones and will need to be addressed by individual institutions, but they are not different in principle from the problems arising from imposing waiting lists (probably universally practised and accepted as a "fact of life"), which can result in substantial suffering and even death.

Why we need a clinical trial for vitamin K

J M Slattery

Vitamin K is given to many babies born in the United Kingdom, but we still do not know if it has substantial hazards. Because the population exposed to vitamin K is very large even quite small hazards would involve many adverse events. It is therefore important to be able to put reasonably close bounds on the potential damage that vitamin K prophylaxis could cause. Past research has not allowed us to do this but a large randomised controlled clinical trial of vitamin K against no vitamin K, enrolling only infants at low risk of haemorrhagic disease, would do so. There is no question that vitamin K is a useful treatment in babies at highest risk of haemorrhagic disease: the question is whether the trend towards use of vitamin K in lower risk babies should be encouraged.

Vitamin K has been widely used for over 30 years as a prophylaxis against haemorrhagic disease of the newborn, but the first case-control study of its long term safety (in terms of the risk of cancer) was not published until August 1992. This suggested that vitamin K given intramuscularly to neonates might double the risk of childhood cancer.¹ More recent Swedish and American studies have not shown similar effects.^{2,3} Of course, all effective treatments carry some risk, and to assess whether widespread use of a particular treatment is warranted we must know both the risk of not treating and the risk of treating. Furthermore, if we can identify groups of neonates with more or less to gain from treatment we must know the risks within each such group. Randomised clinical trials are by far the most reliable method of assessing the balance of risks and benefits of treatments but a major difficulty is finding a form of clinical trial that is informative, practicable, and acceptable to parents and medical staff. It is most unlikely that a trial in infants at high risk of haemorrhage would ever be considered ethical unless convincing evidence of adverse effects was discovered. In this paper I argue that, among infants at low risk of haemorrhagic disease, we are never likely to discover the true balance of risks and benefits but that a well designed large clinical trial could provide acceptable bounds to our present state of ignorance and provide better information to allow parents to make an informed choice of treatments.

Clinical research

The largest clinical studies of vitamin K were carried out nearly 50 years ago. A review by Dam *et al* reports the work of Dyggve who compared the clinical outcome for 11 000 babies whose mothers were given oral vitamin K within 48 hours of the birth with 22 000 controls.⁴ Lehmann compared 13 250 babies given oral vitamin K with 17 740 historical controls.⁵ Neither study was a randomised controlled trial, but both had large untreated groups that provided estimates of

incidence. Lehmann's primary clinical outcome was death from haemorrhage while Dyggve reported all haemorrhages. This difference complicates comparison of the studies, but where comparable measurements were made the results were quite different. For instance, in combined treatment and control groups Dyggve reported 411/33 247 (1.23%) deaths from intracranial haemorrhage, and Lehmann reported 54/30 950 (0.17%). The control group frequencies from these studies were 4.2 haemorrhagic deaths per 1000 (Lehmann) and 36.3 haemorrhages per 1000 (Dyggve). The sevenfold difference in mortality from intracranial haemorrhage leads us to view these figures with caution, but there were clear differences between the studies that might explain this; for instance, Lehmann selected infants weighing over 2500 g while Dyggve could not have applied such a criterion since treatment was antenatal. Both studies found a statistically significant and clinically important reduction in haemorrhage in treated babies, but neither reported any long term follow up necessary to pick up a side effect such as cancer. Lehmann's study is more relevant to current clinical practice since vitamin K was given directly to the infant.

There have been surprisingly few recent studies, and the Oxford Database of Perinatal Trials lists only two which measured a clinical outcome.^{6,7} Vietti *et al* restricted their study to bleeding complications after circumcision within days of birth, and hence it shed little light on the desirability of prophylaxis for infants with low risk of haemorrhage.⁶ Sutherland *et al* randomised 3338 infants into three groups: placebo, 0.1 mg menadione, or 5 mg menadione given intramuscularly.⁷ The babies were of normal birth weight (more than 2260 g), and so this study is comparable with that of Lehmann. Any bleeding within the first four or five days of life was recorded: 86/1143 (7.5%) with placebo, 60/1132 (5.3%) with 0.1 mg menadione and 61/1063 (5.7%) with 5 mg menadione. The two doses of vitamin K were equally effective even though one was 50 times smaller than the other. Of these bleeds, 68% were associated with circumcision and many were fairly minor. There were eight serious bleeds in the placebo group (0.7%) and none in either treated group. Four of these eight were associated with circumcision so that an estimate of serious bleeding in normal birthweight, uncircumcised infants is 3.5 per 1000.

I have concentrated on haemorrhages with a lasting impact on the health of the child because I am assuming that the adverse effect we are most likely to be interested in is cancer. Hence, the benefit we should consider is avoidance of a similarly serious disease.

Late haemorrhagic disease

Haemorrhages more than a week after birth were not well documented before the introduction of prophylaxis.

Department of Clinical
Neurosciences, University
of Edinburgh, Edinburgh
EH4 2XU
J M Slattery, medical
statistician

BMJ 1994;308:908-10

lactic vitamin K, and thus it is difficult to estimate the incidence in untreated populations or to gauge their importance when planning clinical trials. The largest observational study was that by Bhanchet *et al*, who documented 93 cases in the Siriraj and Ramathibodi hospitals in Bangkok between 1950 and 1975.⁸ Rough calculations based on local demographic details (Dr S Boonyakarnkul, personal communication) suggest a frequency of about 1.7 per 10 000. About 35% of babies in these hospitals now receive vitamin K, and presumably fewer did so 30 years ago. This figure would substantially affect estimates of total haemorrhagic disease only in babies at low risk of the early disease. As we will see, the risk of late haemorrhagic disease in these infants is also low—lower than the above estimate—and has been estimated separately in a recent study.

Late onset disease is more serious than early: Bhanchet found that in 63% of cases the infant suffered intracranial haemorrhage and 35% died. However, it has at least one risk factor in common with early onset disease: Bhanchet reported that in 98% of cases the infants had been breast fed, and another study found that in all 23 cases infants were breast fed.⁹ The prevalence of breast feeding in all infants was not reported, but the authors regarded their finding as unusual enough to merit comment.

Risk factors for haemorrhage

The research considered so far has given estimates of haemorrhagic disease in treated and untreated infants from fairly heterogeneous populations. Researchers have remarked, however, that high and low risk infants can be discriminated on the basis of clinical and social observations.^{4,7} Surgical procedures, asphyxia during birth, prolonged labour, a high degree of albuminuria in the mother, and breast feeding are commonly cited factors increasing risk. Sutherland⁷ cited researchers who claimed that severe hypoprothrombinaemia can be avoided by supplementary feeding during the first few days of life. The importance of these risk factors is that, if side effects of the treatment exist, the benefits of treatment may outweigh the risks only in infants at high risk of haemorrhage.

Frequency in low risk groups

To design a study to justify applying vitamin K universally we have to know the risk of haemorrhage in low risk groups that can be identified at birth. This risk can be estimated with data from surveys by McNinch and Tripp, who examined the rates of haemorrhagic disease in British infants by treatment policies in major maternity units over two years,¹⁰ and Handel and Tripp, who estimated numbers of births in maternity units by treatment policies (intramuscular vitamin K, oral vitamin K with intramuscular administration in selected cases, and no vitamin K in general but with treatment in selected cases).¹¹ Twenty seven cases of haemorrhagic disease were found among 1 670 000 births. Ten were serious or fatal: five babies who had received oral vitamin K and five who had had no vitamin K. All 10 were breast fed and presented more than a week after birth. Handel and Tripp's survey suggests that the ratio of intramuscularly treated babies to orally treated babies to untreated babies was about 4.3:2.2:1.0. This gives frequencies of fatal or disabling haemorrhages of 2.2 per 100 000 for untreated babies (babies born in units where low risk babies are untreated) and 1.0 per 100 000 for orally treated babies.

These results show how successful is the selection of high risk babies in units that do not practise universal prophylaxis. Infants considered to be at high risk by

attending clinicians are treated everywhere, and hence frequencies are underestimates of the natural incidence of the disease. However, even if as many as half of infants born in units where treatment is not universal are in fact treated because they are deemed to be high risk the risk of serious haemorrhage in the group of low risk untreated infants is only about 4 in 100 000. Handel and Tripp also examined changes in treatment policy since 1982: a pronounced trend was observed towards treatment of infants with low risk of bleeding. Does this matter? Could there be a hazard associated with this policy?

Is there a risk of cancer from vitamin K?

After two case-control studies and one large retrospective cohort study there is still considerable disagreement on whether vitamin K causes cancer. Case-control studies are always open to criticism about the selection of controls, and all retrospective studies rely on an assumption that we can correct for or ignore selection bias in treatment. In view of the very small effects we wish to investigate I doubt whether we could ever justify such an assumption and so provide unassailable safety data for vitamin K. No case-control studies have looked at safety with respect to diseases other than cancer. The evidence from routine morbidity statistics is also unclear. Golding *et al* cited leukaemia registration rates as corroborative evidence,¹ while Miller cited an American survey purporting to refute such a connection.¹² Draper and Stiller compared leukaemia rates with sales of phytomenadione in the United Kingdom.¹³ There are inherent difficulties in interpreting such evidence. Consider the cancer registration rates from 1955 to 1985 in England and Wales by age groups 0-4, 5-14, and 15-24 (figure). The

Rates of cancer registration by age group in England and Wales. Data from the World Health Organisation¹⁴ and Office of Population Censuses and Surveys¹⁵

registration rate for children aged 0-4 increased substantially from 1955 to about 1963, and this may correspond with the introduction of vitamin K treatment. An increase is also seen, however, in the group aged 15-24 during the same period (and in higher age groups, data not shown), and it is unlikely that these people would have received vitamin K. Such uncontrolled data are at best circumstantial evidence and certainly not a secure basis for medical policy decisions.

What could a clinical trial achieve?

At present we know that vitamin K protects against haemorrhagic disease and we know the risk of this disease in low risk infants; we know the achievable benefits of treatment, but we do not know the hazards. Thus research need only evaluate the hazards not the benefits. There are several advantages to using a randomised controlled trial for this problem. Firstly, it

is the form of research most likely to convince clinicians; secondly, we can specify the precision with which we wish to know the answer; thirdly, if future objections are raised to vitamin K we have a known population in which they can be investigated without bias; and, fourthly, prognostic factors can be recorded on entry rather than having to rely on medical records.

There are two problems: clinicians should only randomise infants for whom there is real doubt about the appropriateness of the treatment, and a trial to detect side effects similar in magnitude to the benefits in low haemorrhagic risk infants would need more than a million infants. The requirement for clinical doubt is perhaps not a problem. McNinch and Tripp showed that justifying a policy of treating all infants is of current clinical interest,¹⁰ and a trial with infants at low risk of haemorrhagic disease should be of interest to many clinicians. If risks of haemorrhage and side effects are not closely related such a trial would also answer the safety question for infants with higher risks of haemorrhage. The question of sample size is more difficult. I believe that we should decide what degree of safety is acceptable and achieve a sample sufficiently large to be able to show this. For a treatment intended for an entire population this is the least we can ethically do. For example, a trial to detect the increase in the cancer rates suggested by Golding *et al*¹ would require 40 000 infants and would also reveal differences in mortality from all causes of about 4/1000. An even larger trial would be required if we wished to test separately the intramuscular and oral routes of administration.

ORGANISING A TRIAL

Such a trial would be simpler to organise than trials of acutely ill patients since prospective parents could

be approached well before the start of the trial to allow time for careful explanation and informed consent. The treatment is available in all maternity units, and no placebo would be necessary since only major events, mortality and cancer, are of interest and these events are distant in time from the treatment. Although follow up of 40 000 children over several years would be difficult, substantial use of existing cancer and death registries could be made.

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(Accepted 29 November 1993)

Current Issues in Cancer

Superficial bladder cancer

R R Hall

This is the fourth in a series of articles examining recent developments in cancer and updating what we know about the disease

Freeman Hospital, High Heaton, Newcastle upon Tyne NE7 7DN
R R Hall, consultant urologist

Series editor: G M Mead.

G M Mead is consultant in medical oncology at the Cancer Research Campaign's Wessex Oncology Medical Unit

BMJ 1994;308:910-3

Bladder cancer is almost certainly a product of the industrial revolution and the cigarette smoking that has accompanied it. Exposure to a chemical bladder carcinogen such as β naphthylamine, benzidine, or 4-diphenylaniline¹ can be proved in only a small proportion of patients and only a handful obtain industrial diseases benefit after developing "Prescribed Industrial Disease C23." None the less, the continued use of known carcinogenic substances in British industry for many years after their identification, the wide range of industries with a known or suspected increased risk of bladder cancer, and our ignorance of the carcinogenic potential of many materials used in current manufacturing should be a cause for continuing concern.

The association between bladder cancer and cigarette smoking, first considered more than 30 years ago,^{1,2} has been confirmed only recently.^{4,5} The incidence of this cancer among workers in "at risk" industries has been shown to be increased if they smoke as well,⁶ and first degree relatives of bladder cancer patients may increase their familial risk if they smoke.⁷ Whether the increased tobacco consumption by young women in recent years will alter the current 3:1 male to female preponderance of this disease and

whether young women can be persuaded to stop smoking for this reason remain to be seen.

Whatever environmental causes may exist, it has been the molecular aetiology of bladder cancer that has attracted most recent attention. As Jones *et al* have explained, "chemical and physical carcinogens leave footprints of their activities on DNA because of the patterns of base changes they induce."⁸ Chromosomes 1, 5, 9, 11, and 17 have shown non-random changes in bladder cancer, and allelic deletions of chromosomes 9 and 17 occur in over 60% of bladder tumours.⁹ Chromosome 9 aberrations have not been reported in any other solid tumour, the deletion of chromosome 17 with its tumour suppressor gene p53 occurs frequently in bladder cancer,¹⁰ and cigarette smoking increases mutagenic DNA changes in bladder tumours.¹¹ "Working from gene to carcinogen is likely to have a profound impact on our understanding of the origins of human [bladder] cancer."⁸

Presentation and diagnosis

Haematuria is well known as the main presenting symptom of bladder cancer but bladder tumours may present with any bladder symptom. Most patients are alarmed by blood in their urine and seek medical advice promptly. Few people suffer increasing fre-