by misclassification of spontaneously resolving cases. Reported rises in perforation rates with duration of symptoms may also be explained by selection bias due to spontaneous resolution of milder inflammation.[15] The perforation rate is therefore worthless as a measure of quality in the management of appendicitis.

That appendicitis commonly resolves implies that future diagnostic and therapeutic policies should aim at early detection and operation in patients with perforating appendicitis or progressive inflammation and at active observation and investigation of alternative diagnoses in other patients. Studies on clinical signs and laboratory findings in relation to the degree of inflammation or perforation have shown promising results.[28,29] The role of explorative laparoscopy in this context is as yet unclear but may increase the yield of alternative diagnoses in prolonged abdominal pain.[30]

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Renal disease and use of topical non-steroidal anti-inflammatory drugs

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Renal impairment is a recognised complication of oral, rectal, and intramuscular non-steroidal anti-inflammatory drugs. We report cases of renal disease associated with a topical preparation.

Case report

CASE 1

A 74 year old woman presented with a six week history of breathlessness and oedema. Investigations showed proteinuria (+++ by dipstick), a serum albumin concentration of 17 g/l, and a creatinine concentration of 169 μmol/l. Her urine contained no leucocytes but grew *Escherichia coli* in culture and she was prescribed trimethoprim, frusemide, and prophylactic heparin. Her renal function deteriorated, and three days later she was transferred to our care. She was not volume depleted but remained grossly nephrotic with proteinuria of 18 g/day. There was no eosinophilia or eosinophiluria, and results of renal phlebography and ultrasonography were normal. Renal biopsy showed a florid interstitial nephritis with normal glomeruli.

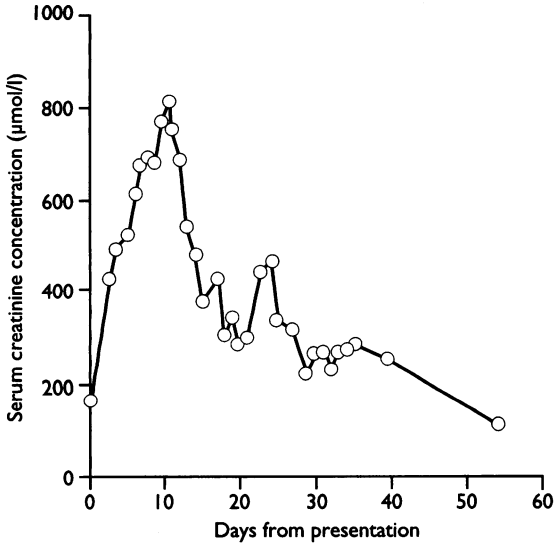
The combination of nephrotic syndrome and interstitial nephritis was highly suggestive of use of non-steroidal anti-inflammatory drugs, but this was denied by the patient, her relatives, and her general practitioner. All drugs were therefore changed or stopped, and she was given high doses of steroids. Her renal function worsened, however, and she started haemodialysis. Shortly afterwards she became confused, possibly because of her uraemia, steroid treatment, or dialysis. A tube of piroxicam gel was then discovered in her locker, which she had been applying regularly to her shoulder and back for musculoskeletal pains. Over six weeks she had used three 60 g tubes of 0·5% piroxicam and had been applying it in the ward bathroom at least twice daily until her confusion. After its removal her renal function rapidly recovered so that 10 days later she stopped dialysis and three weeks later her oedema was reduced with proteinuria only +, serum albumin concentration 32 g/l, and creatinine concentration 110 μmol/l. The figure shows the changes in creatinine concentration over time.

CASE 2

A 57 year old woman had been using a topical cream of 3% benzydamine hydrochloride for four months and had used a total of 400 g of cream. She was referred for investigation of plasma concentrations of creatinine and urea of 137 μmol and 13·2 mmol/l respectively. When the drug was stopped these concentrations fell to 96 μmol/l and 6·5 mmol respectively, results consistent with the drug causing a substantial reduction in glomerular filtration rates. No other cause was found.

Comment

About 5-18% of outpatients taking non-steroidal anti-inflammatory drugs have renal impairment.[1] Case-control studies suggest that use of these drugs doubles the risk of renal disease; in men aged over 65



Serum creatinine concentration of patient (case 1) rose until start of dialysis. During this time topical treatment with piroxicam stopped, and renal function rapidly improved

the risk increases tenfold.[2] Risk factors include age, volume depletion, pre-existing renal impairment, and other high renin states such as heart failure and cirrhosis. Inhibition of tonic prostaglandin dependent renal vasodilatation reduces the glomerular filtration rate and may lead to acute renal failure. Other effects include sodium and water retention, hyperkalaemia, hypertension, and medullary ischaemia, sometimes sufficient to cause papillary necrosis.

Nephrotic syndrome can occur with or without interstitial nephritis, but the combination is characteristic of the use of non-steroidal anti-inflammatory drugs.[3] Allergic features such as rash, eosinophilia, or eosinophiluria are usually absent. Prognosis is good if the drug is stopped, and in a review of 56 cases steroids gave no clear benefit.[3] The development of nephrotic syndrome does not seem dose dependent, and most non-steroidal anti-inflammatory drugs, including piroxicam, have been implicated.[4] In healthy volunteers daily topical treatment with 2 g of 0·5% piroxicam gel for 14 days gave a blood concentration that was 5% of that achieved by the standard oral dose.[5] Elderly patients might achieve higher blood concentrations because of reduced drug clearance, thin skin, and frequent application of the drug over large areas.

The first case demonstrates that topical non-steroidal anti-inflammatory drugs may cause considerable systemic side effects. The renal lesion seen is highly specific for non-steroidal anti-inflammatory drugs and strongly suggests that the piroxicam was responsible. A complete drug history must include questions on the use of topical preparations.

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Formal measurement of clinical uncertainty: prelude to a trial in perinatal medicine

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Clinical trials are ethical when there is collective and balanced uncertainty about the best treatment among informed clinicians. This uncertainty can be identified either by observing differences in practice or, as explored here, by formal measurement of clinical belief.

Fetomaternal medicine is largely concerned with timing delivery of preterm fetuses that are failing to thrive. Delivery is indicated when prematurity is judged preferable to continued intrauterine life, but often the relative risks of these alternatives are unknown.[1] During the planning of a trial to compare early with delayed delivery under different circumstances 10 specialists in fetomaternal medicine were interviewed about their beliefs.

Methods and results

The specialists were presented with four scenarios, one practice and three substantive, in each of which the decision between immediate and delayed delivery was difficult (see figure). They recorded their opinions on an analogue dial connected to a microcomputer. For each scenario respondents were asked what they thought the relative risk of permanent morbidity was most likely to be in a hypothetical and infinitely large randomised trial in similar patients. An answer of 1 indicated that their best guess was that such a trial would show no difference between immediate or delayed delivery, an answer of 0·5 that the chance of morbidity would be halved by immediate delivery, and an answer of 2 that it would be doubled. Respondents were then asked what they would regard as a surprisingly good or bad result in the hypothetical trial—that is, when they believed that there was only a one in 40 (2·5%) chance of a result being equally or more extreme. These ranges of expected results gave a measure of the respondents' confidence in their own beliefs. To familiarise participants the answers were displayed during the practice scenario, but they were concealed for the three substantive scenarios.

For each scenario the mean result considered to be most likely was close to 1, with a wide scatter in the individual results—for example, from a 75% decrease to a 25% increase in the risk to a fetus delivered early in the practice scenario (figure). This shows that the scenarios caused collective uncertainty. The mean of all the estimates of surprisingly good and bad results was roughly a reduction and increase in risk of around 50% respectively. All 10 respondents had individual ranges of expected results that included 1 on scenario 1. One was included for six respondents on scenario 2 and for eight respondents on scenario 3.

Comment

These results show that experts do not agree about the benefit of delivery for preterm fetuses that are failing to thrive but are not thought to be near to death. For babies such as those described there is collective and reasonably balanced uncertainty[2]—the main requirement for a randomised trial.[3] It is fortunate that clinicians given the same inconclusive information form different views because these differences provide the impetus for clinical trials. Our results also show, however, that some clinicians are in two minds when others have strong expectations of either benefit or harm. This makes agreement on fixed entry criteria unlikely and suggests that individual balanced un-