

unacceptable disrespect for early human life. Perhaps a distinction has to be drawn between deliberately risking the induction of multiple pregnancy with the full intention of using fetal reduction and resorting to fetal reduction only when high order multiple pregnancy occurs inadvertently.

There is no information on the emotional consequences of selective reduction on the mother or the surviving children. In a short time mothers go from the emotional problems of prolonged infertility to high order multiple pregnancy and fetal reduction. Initially, they may experience relief after selective reduction, but they may later have feelings of guilt or bereavement. Careful follow up is required.

Fetal reduction is an example of technical advance moving ahead of public opinion, and open discussion of the obstetric, legal, and ethical issues is required before the practice can be fully accepted. Clearly, prevention is better than cure, and everything should be done to prevent the dilemma for parents in the first place. It may well come to be recognised, however, that selective fetal reduction is the humane option for some

couples faced with the horrifying potential consequences of multiple births.

PETER W HOWIE

Professor of Obstetrics and Gynaecology,  
Ninewells Hospital and Medical School,  
Dundee DD1 9SY

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## Intra-arterial hepatic chemotherapy for liver malignancy

### *Not yet proved to prolong survival*

The rationale for giving patients with tumours of the liver intra-arterial hepatic chemotherapy is anatomical, pharmacological, and toxicological. The blood supply to liver tumours derives mainly from the hepatic arterial bed, and consequently more drug should reach the tumour if given by this route rather than either systemically or into the portal circulation.<sup>1-3</sup> Using drugs with short plasma half lives that can be efficiently extracted by the liver should diminish systemic toxicity, and the ability to deliver high local concentrations of drug may increase the regression of tumours.<sup>4</sup> Giving drugs by infusion and decreasing hepatic arterial flow may further enhance toxicity.<sup>5</sup> Concomitant injection of inert particulate matter—for example, biodegradable starch microspheres—may not only decrease blood flow but also infarct the tumour.<sup>6</sup> A recent advance has been to show the prolonged retention in sites of metastatic tumour of lipophilic cytotoxic drugs injected in lipid contrast medium.<sup>7</sup>

Numerous non-randomised studies of intra-arterial hepatic chemotherapy in primary and secondary liver cancer have been conducted since the technique was described in the early 1950s.<sup>8,9</sup> Higher rates of response than for systemic chemotherapy have been seen in patients with hepatoma,<sup>10</sup> metastatic ocular melanoma,<sup>11</sup> and metastatic colorectal carcinoma.<sup>12</sup> But randomised studies are needed to determine toxicity, rates of response, and the benefits to survival. So far randomised studies have been reported only for metastatic colorectal carcinoma.

The California Oncology Group compared systemic and intra-arterial fluorouracil in 61 patients with liver metastases of colorectal carcinoma and found no difference in rate of response or survival.<sup>13</sup> Two separate trials—from the Memorial Sloan Kettering Cancer Research Centre and the Northern California Oncology Group—have used floxuridine and shown a higher rate of response (50-59%) with intra-arterial hepatic chemotherapy than with systemic chemotherapy (10-17%).<sup>14,15</sup> Patients failing to respond to systemic chemotherapy were crossed over to intra-arterial hepatic chemotherapy, and up to a quarter responded further. The crossover made true assessment of survival impossible,

but this was not the primary aim of the trials. In the trial at the Sloan Kettering the median survival of the patients starting treatment with intra-arterial hepatic chemotherapy was 17 months compared with 12 months for those starting treatment with systemic chemotherapy. This difference was not significant but may show some survival benefit in certain subgroups of patients—for example, those not prone to developing extrahepatic disease. The main toxicity of intra-arterial hepatic chemotherapy was chemical hepatitis, biliary sclerosis, and gastroduodenal ulceration. Some patients had liver pain, but abdominal pain was more common and was caused by misperfusion of the gastrointestinal tract. Indeed, systemic infusional chemotherapy was associated with greater toxicity, especially diarrhoea, and the overall quality of life of patients given intra-arterial hepatic chemotherapy was judged to be better than that of those given systemic chemotherapy.<sup>14</sup> An important problem, however, has been the higher rate of extrahepatic metastases in those given intra-arterial hepatic chemotherapy.

The morbidity caused by intra-arterial hepatic chemotherapy has decreased with experience of the technique.<sup>16</sup> Ambulatory patients may be treated with internally or externally placed pumps.<sup>17</sup> One important factor limiting the use of intra-arterial hepatic chemotherapy is the lack of effective drugs to treat tumours such as hepatoma and colorectal carcinoma; other factors include cost and the continued growth of disease in other sites.

S T A MALIK

Clinical Research Fellow,  
Imperial Cancer Research Fund,  
London WC2A 3PX

P F M WRIGLEY

Consultant Oncologist,  
Imperial Cancer Research Fund,  
Department of Medical Oncology,  
St Bartholomew's Hospital,  
London EC1A 4BE

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## Depression resistant to tricyclic antidepressants

### *Adding lithium will often work*

Up to a third of patients with major depression either fail to respond or respond only partially to treatment with tricyclic antidepressants.<sup>1</sup> In some cases specific psychotherapeutic or social intervention will be required, but further drug treatment will be considered for many. What are the possibilities?

An initial step is to see whether the dose of the tricyclic antidepressant may be increased. The proportion of patients responding increases as the dose is raised, and many patients may be able to tolerate more than the usual 150 mg daily.<sup>2</sup> Whether monitoring plasma concentrations of tricyclic antidepressants can help determine correct dosage is disputed,<sup>3,4</sup> and the usual course is to increase the dose until definite but tolerable side effects are apparent.<sup>5</sup>

For patients with severe depression, when endogenous symptoms are prominent, the usual practice when treatment with tricyclic antidepressants is ineffective is to consider electroconvulsive therapy. At least half of this group of patients will improve after electroconvulsive therapy.<sup>6,7</sup> Subjects who are not responding to unilateral electroconvulsive therapy should have a trial of bilateral treatment before electroconvulsive therapy is abandoned.<sup>8</sup> Electroconvulsive therapy is particularly useful in patients with psychotic depression, but in such patients combining tricyclic antidepressants with neuroleptic drugs may yield rates of response similar to those with electroconvulsive therapy (about 80%).<sup>9</sup>

Electroconvulsive therapy usually necessitates admission to hospital, and many patients are reluctant to receive it. There is thus much interest in alternative drug treatments, and recent attention has focused on the use of lithium. Two controlled investigations have suggested that adding lithium to tricyclic antidepressants in patients who have not responded produces a clear improvement in about 50-60%.<sup>10,11</sup> Although some may respond within two to three days, the more usual pattern is for a gradual remission over about three weeks while lithium concentrations are maintained between 0.5-0.8 mmol/l.<sup>12</sup> Whether this response is attributable to an antidepressant action of lithium alone<sup>13</sup> or to a synergism between lithium and the tricyclic antidepressant is not clear.<sup>11,14</sup>

Ineffective treatment with tricyclic antidepressants may also be supplemented by a small daily dose of liothyronine (triiodothyronine) (20-40 µg). Both anecdotal reports and one controlled trial suggest that 60-70% of patients may show some improvement within a few days.<sup>15</sup> Recent assessments

have, however, been less encouraging,<sup>16,17</sup> and adding lithium is probably a more effective strategy.<sup>17</sup>

If a patient has been able to tolerate a full dose of a tricyclic antidepressant with no improvement changing to another tricyclic antidepressant or a newer antidepressant will probably not be worth while. If combined treatment with lithium and tricyclic antidepressants has been ineffective a monoamine oxidase inhibitor should be considered. Given in high enough doses monoamine oxidase inhibitors are effective antidepressants,<sup>18</sup> and they often help in patients who have failed to respond to other antidepressants and electroconvulsive therapy.<sup>18,19</sup> It was originally suggested that depressed patients who responded to monoamine oxidase inhibitors were more likely to have an atypical presentation of depression,<sup>20</sup> and the results of some, but not all, recent investigations have supported this proposal.<sup>18,21</sup> The balance of evidence shows that patients whose depressive disorder is characterised by mood reactivity, increased sleep and appetite, and feelings of anxiety and anger will show a good rate of response (about 70%) to monoamine oxidase inhibitors.<sup>22</sup> Clinical impression is that such patients are unlikely to be helped by electroconvulsive therapy.<sup>5</sup>

Lithium may also potentiate treatment with monoamine oxidase inhibitors, and there are reports that lithium and tranylcypromine may relieve severe depressive states that have not responded to lithium and a tricyclic antidepressant combined or to a monoamine oxidase inhibitor given alone.<sup>23</sup> Some believe that adding tryptophan to lithium and a monoamine oxidase inhibitor may help in patients with particularly resistant depression, and about half of this group of patients may show substantial improvement with this combination.<sup>24</sup> Good clinical effects have also been reported with combining lithium, tryptophan, and clomipramine.<sup>25</sup>

The drugs considered most effective in resistant depression are characterised by their ability to produce a striking enhancement in some aspects of brain serotonin function.<sup>14,23,24</sup> There has been much progress recently in identifying specific subtypes of brain serotonin receptors,<sup>26</sup> and selective drugs for these receptors are becoming available. Whether such drugs have useful antidepressant properties will therefore be of both clinical and scientific interest.

P J COWEN

Medical Research Council Clinical Scientist,  
Medical Research Council Unit of Clinical Pharmacology,  
Littlemore Hospital,  
Oxford OX4 4XN