Magnesium for preventing and treating eclampsia: time for international action

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Every minute, a woman dies in pregnancy or childbirth, and 99 out of every 100 of these women live in developing countries. Among deaths from causes other than abortion which are directly attributable to complications of pregnancy, about a quarter are associated with pre-eclampsia/eclampsia. Partly because the aetiology of the syndrome has remained obscure, many different approaches have been used to try to prevent and manage it. One of these—magnesium sulphate as an anticonvulsant—was introduced to obstetric practice in the USA almost a century ago, and until recently, the drug was mainly used there and in countries where American obstetric teaching had been influential. One reason that magnesium sulphate was not used more widely was the lack of reliable empirical evidence of its effects from controlled trials; another was that some critics maintained that no theory existed to explain how magnesium sulphate could be helpful in eclampsia. 7 years ago, a study dubbed by one commentator as the most important obstetric randomised trial of the 20th century showed that, of three common approaches to controlling eclamptic convulsions, magnesium sulphate was the most effective. The Collaborative Eclampsia Trial was a landmark in several respects: the participation of 1687 women and their carers in 27 hospitals in nine developing countries achieved more than all the small-scale poorly controlled investigations over the previous 50 years, mainly in the countries in which only 1% of the world’s cases of eclampsia occur. The report of the trial had a dramatic effect on practice in the UK, one of the countries in which magnesium sulphate had not been widely used by obstetricians. The trial is a good example of how collaborations between the developing and developed worlds can lead to improved clinical practice.

Despite the fact that the mode of action of magnesium sulphate remains obscure, the results of the Collaborative Eclampsia Trial prompted speculation about whether the drug might prevent eclampsia developing in women with pre-eclampsia. A systematic review of evidence from controlled trials involving women with pre-eclampsia showed that magnesium sulphate was the most promising among the alternative anticonvulsants studied, but the data were sparse (37 eclampsia endpoints in total) and not sufficiently robust as a guide to practice. Evidence published in today’s Lancet strengthens beyond reasonable doubt the suggestive evidence from the systematic review. The Magpie Trial, which involved 10 141 women with pre-eclampsia and their carers in 175 hospitals in 33 countries, shows that magnesium sulphate reduces the risks of eclampsia among women with pre-eclampsia. Like the evidence generated by the Collaborative Eclampsia Trial, the evidence from the Magpie Trial is of great relevance to the care of women all over the world. It is now clear that magnesium sulphate has a very important role in preventing as well as controlling eclampsia, and the available evidence suggests that it is tolerably safe. Importantly, the drug is very cheap—it need cost no more that US$5 per patient.

In theory, hundreds of thousands of women could benefit from the evidence yielded by these two studies. In many places, however, the health-service infrastructure needed to respond to eclampsia and the signs and symptoms of pre-eclampsia simply does not exist. Furthermore, even if women are transferred successfully to appropriate health-care facilities, magnesium sulphate may not be available.

Women, clinicians, and researchers have now collaborated in producing reliable evidence showing that magnesium sulphate can prevent as well as control eclamptic convulsions. It is now up to those responsible for maternal health services—at local, national, and international levels—to ensure that this effective, apparently safe, and inexpensive drug is available to women everywhere when needed.

As the organisation that initiated the Collaborative Eclampsia Trial, WHO has the power to take up this particular responsibility. In 1995, the report of that trial stated: “From magnesium sulphate first being suggested for women with eclampsia (1906) to the introduction of diazepam (in 1968), a possible 33 million women would have had an eclamptic convolution and 3 million of them may have died. Up to 1987, when phenytoin was introduced, a further 9 million possibly had an eclamptic convolution and one million died.” Unknown numbers of women with eclamptic convulsions have had eclamptic convulsions over the past 7 years simply because magnesium sulphate was not available to them.

5 years after the report of the Collaborative Eclampsia Trial, the importance of magnesium sulphate was formally acknowledged in a document published by WHO, UNFPA, UNICEF, and the World Bank; but unfortunately publication cannot ensure that magnesium sulphate is available to women whose lives may depend on it. As implied by the “bedrock principle”
of securing “universal access to quality care”,10 WHO and other international organisations need to play their part in ensuring that women with pre-eclampsia and eclampsia have access to magnesium sulphate. For its part, WHO could make sure that evidence about the important beneficial effects of the drug is disseminated effectively to ministries of health, and that it is registered and available in all countries. Other organisations—eg, the World Bank and charitable foundations—could fund the provision and distribution of the treatment kits that proved so popular and effective in both of the controlled trials of magnesium sulphate. Still other international organisations—eg, the International Federation of Gynecology and Obstetrics and the International Confederation of Midwives—could help to make sure that front-line clinicians are trained to use the drug. It is time for concerted international action to ensure that women all over the world benefit from the results of the important research on magnesium sulphate.

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4 Chalmers I, Grant A. Salutary lesson from the Collaborative Eclampsia Trial. Lancet 1998; 352: 1868–89.

Translocations at 11q23 in childhood ALL: age under 1 and poor prognosis

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Rearrangements of the chromosome locus 11 band q23 are among the more common cytogenetic abnormalities seen in acute leukaemia. They occur in about 10% of acute lymphoblastic leukaemias, 5% of acute myeloid leukaemias, and 85% of the secondary leukaemias, usually the M4 or M5 subtypes of acute myeloid leukaemia, which develop as a consequence of treatment with topoisomerase II inhibitors.2 Although more than 50 reciprocal chromosomal loci have been described in 11q23 translocations, the most common are t(4;11)(q21;q23), t(9;11)(p22;q23), and t(11;19) (q23;p13). Newer molecular genetic methods are more sensitive than the conventional chromosome-banding techniques. Multiplex RT-PCR is the method of choice for screening, as it can simultaneously detect several fusion partner genes associated with the known translocations.2 Fluorescence-in-situ hybridisation, assays have been developed to detect the common fusion transcripts involving the MLL (mixed-lineage-leukaemia) gene. However, only Southern blotting can detect all MLL gene rearrangements. With modern molecular techniques, MLL rearrangements have been demonstrated in up to 80% of infants with acute lymphoblastic leukaemia, including many that do not have cytogenetically detectable 11q23 abnormalities.3

Most 11q23 translocations, but not all, disrupt the MLL, which encodes a protein of 3968 amino acids. The MLL protein contains two central zinc-finger domains and a 210-aminoacid C-terminal segment. The N-terminal region of MLL contains three A-T hook motifs. In MLL, the A-T hook motifs and the zinc-finger domains are separated by a 47-aminoacid region with homology to domains of human DNA-methyltransferase, which produces fully methylated double-stranded DNA from a hemimethylated substrate. The structural features of MLL suggest that its normal physiological function, as well as its role in leukaemogenesis, may be mediated by direct interaction with DNA.

The translocations t(4;11), t(9;11), and t(11;19) fuse MLL to a family of genes, AF-4, AF-9, and ENL, respectively, which may contribute similar functional domains to the resulting chimeric proteins. AF-4 encodes a protein that contains a nuclear-targeting sequence and is widely expressed in normal tissues. AF-9 and ENL also encode proteins that contain nuclear-targeting signals and all three proteins are rich in serine and proline, suggesting that they may function as transcriptional transactivators.4 The evidence that MLL fusions are important in the development of leukaemia was established by the creation of chimeric mice which expressed MLL-AF9 and went on to develop acute myeloid leukaemia after 4–12 months, with a phenotype similar to that seen in patients with t(9;11).5 Similar results have been obtained by the retroviral transduction of MLL-ENL into haemopoietic cells,4 11q23 rearrangements are generally thought to impart a poor prognosis and the report by Chin-Hon Pui and colleagues in this issue of The Lancet dissects out possible confounding variables: in particular, age at diagnosis, a well known prognostic factor in childhood leukaemia, and the specific subtype of cytogenetic abnormality on 11q. The international authorship of this large retrospective study reflects a healthy transatlantic collaboration among paediatric haematologists with a particular interest in this form of leukaemia.

The largest group of patients were those with t(4;11)-positive acute lymphoblastic leukaemia, where the numbers were sufficient to analyse the effect of age and type of treatment on outcome (149 patients under 1 year of age, 58 age 1 to <10 years, and 45 patients >10 years of age). Age under 1 year had an adverse effect on 5-year event-free survival (19%, SE 3%) in infants with this particular translocation, compared with 43% (7%) in 1–9-year-olds. Among the infants, there were no statistically significant differences in treatment outcome among the various cytogenetic subgroups. However, in older children there was a statistically significant difference between the cytogenetic subgroups, and those with t(4;11) had a worse outcome than those with other cytogenetic lesions except for t(9;11). t(9; 11) appears, however, to confer a relatively favourable prognosis.

The inevitable consequence of reporting on cases with these particular subtypes of acute lymphoblastic leukaemia diagnosed between 1983 and 1995 is not only that older cytogenetic techniques were used for diagnosis, but also that different treatment regimens were used at the various participating centres. Most very