Withdrawal of older anticonvulsants for management of status epilepticus: implications for resource-poor countries

Status epilepticus is a common neurological emergency in children admitted to hospitals in resource-poor countries where it has a high mortality and is associated with a significant morbidity. In the last 5 years, some pharmaceutical companies have announced their intention to stop manufacturing parenteral preparations of phenobarbitone and chlormethaziole, and the supply of paraldehyde has been erratic. Paraldehyde and phenobarbitone are recommended for the management of status epilepticus in the recently published *Advanced Paediatric Life Support* guidelines.[1] Their withdrawal would have serious repercussions for the management of status epilepticus in resource-poor countries as these drugs are relatively cheap and easy to administer in these settings.

In particular, the withdrawal of parenteral phenobarbitone is a matter of particular concern. Phenobarbitone is cheap and widely available. It can be administered by slow intravenous push (over 10min) or intramuscularly,[2] a route that is often used in resource-poor countries. The main side effects are respiratory depression and lowering of blood pressure, the development of which depend on the underlying disease and the rate of rise of blood levels. Accordingly, it can be and is used at all levels of hospital care. Therefore, we support the *Advanced Paediatric Life Support* guidelines and have recommended the use of phenobarbitone for third line treatment in the management of status epilepticus in resource-poor countries.[3,4]

If parenteral phenobarbitone is withdrawn, what are the alternatives? Lorazepam or other benzodiazepines are associated with increased risk of respiratory depression and the risk will be increased if benzodiazepines are used as first line treatment. Phenytoin is the alternative agent to phenobarbitone in the *Advanced Paediatric Life Support* algorithm. Intravenous phenytoin is associated with fatal haemodynamic complications, serious skin reactions at the injection site, and cardiac arrhythmias. The agent should be administered into a large vein (but ideally not central) via a slow infusion over 30 minutes through a syringe driver, with the child having cardiac monitoring. These facilities for safe administration are often not available in hospitals in resource-poor countries and, even if they were, following the guidelines for the administration of phenytoin takes three times as long as the slow push of phenobarbitone. This may increase the risk of refractory status epilepticus, which is associated with subsequent brain damage. Furthermore, the *Advanced Paediatric Life Support* guidelines recommend measuring levels 60 to 90 minutes after completion of the infusion, but this assay is only available in a few tertiary or research centres in resource-poor countries. Parenteral phenytoin, though more economical than the newer anticonvulsants, is still four times the cost of parenteral phenobarbitone.

Similarly, paraldehyde is useful in resource-poor settings as it can be given rectally or intramuscularly, appears to prevent recurrence of seizures more often than diazepam, and may be associated with less respiratory depression (Ogutu et al., forthcoming). Although an interaction has been documented with some plastic syringes, this appears to be insignificant with modern syringes when the drug is administered within 10 minutes of it being drawn into the syringe (Ogutu personal communication, 2004). However, the supply of paraldehyde is variable and, as there appears to be only one manufacturer, the price has risen substantially.

Although pharmaceutical companies may not make substantial profits from the manufacture of phenobarbitone, withdrawal of this drug is likely to have a devastating effect on the outcome of status epilepticus in resource-poor countries. The withdrawal of the other drugs used in the treatment of status epilepticus is less clear, but needs to be explored before the manufacture of these drugs is stopped.

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