Sugar treatment doesn't pacify those concerned about preemies

MONTREAL—Preterm and critically ill newborns admitted to neonatal intensive care units often receive pacifiers coated in sucrose to ease their pain. Research has shown that sucrose reduces babies' crying time and improves other behavioral measures of pain. As a result, some investigators insist that withholding sugar from babies enrolled in clinical trials is cruel and unethical.

Although pain researchers currently lack evidence that sugar directly relieves neonatal pain, many say that sucrose's calming effects on infants suggest that it might. "I don't think we can just dismiss behavior as an indicator of pain," says Bonnie Stevens, associate chief of nursing research at the Hospital for Sick Children in Toronto, who, earlier this year, published a meta-analysis of nearly 3,500 infants reporting that sucrose was safe and effective at reducing clinical pain indicators for single painful procedures (*Cochrane Database Syst. Rev.* **20**, CD001069, 2010).

On the basis of behavioral and physiological data, many institutional review boards, especially in North America, are no longer approving neonatal pain trials that include water-based placebo treatments. "I myself will not do a no-treatment control anymore, because I think it's unethical not to give babies something for a painful procedure. I did, but not anymore," says Celeste Johnston of McGill University in Montreal, echoing statements she made at the World Congress on Pain here last month. "If we know there are consequences to pain and we know that sucrose works, then why would we have a no-treatment control?"

The question is a tricky one. A new study casts doubt on whether sucrose actually provides pain relief or simply acts as a sedative and masks the symptoms of neonatal pain. A team led by Maria Fitzgerald, a developmental neurobiologist at University College London, measured the pain-specific brain activity of 59 newborns given either sucrose or water just before getting their heels pricked for a blood test. Reporting online last month, they found no difference in the brain circuitry (measured by electroencephalography), even though babies who sucked on sucrose showed fewer outward signs of pain (*Lancet*, doi:10.1016/S0140-6736(10)61303-7, 2010).

"Sucrose doesn't change the information that's reaching the brain," says Fitzgerald. "If you provide temporary soothing, you'd be fooled into thinking that painful imprinting isn't happening when it actually is."

Ruth Grunau from the Child and Family Research Institute in Vancouver, British Columbia adds that the effects of repeated exposure to the sugar remain understudied in humans. Preemies are sometimes exposed to more than a dozen painful skin-breaking blood collections per day, and receiving a few drops of sugar for each procedure could cause dangerous neurodevelopmental side effects. As such, she says, "teaching parents how to provide support and promoting environmental"—rather than chemical—"support for routine blood collections would be a great advance."

What's more, the molecular data on sucrose's mode of action, stemming from animal models, remain ambiguous. Some studies have singled out opioid pathways, consistent with analgesic effects, but others have implicated dopamine and hormone pathways, which affect attention and motor function but not pain responses.

Despite the uncertainties, Stevens says it's premature to stop providing sucrose. But, she emphasizes, using sucrose is only part of a larger pain management strategy for infants that includes nondrug interventions such as soothers, swaddling and skin-to-skin contact, also known 'kangaroo care'. "What we're always striving for is a balance between the consequences of untreated pain and trying to treat pain in the safest and most effective ways that we can," she says.

Elie Dolgin

'Pay-for-delay' decision may be left to lawmakers

In the US, the question of whether or not pharmaceutical companies should be able to pay off competitors challenging their patent exclusivity may now be left to Congress.

"The effort has been fought to a stalemate in the courts," says Lauren Fuller, director of legislative affairs for the Academy of Managed Care Pharmacy, a managed-care advocacy group that supports outlawing such 'pay-for-delay' deals. "We need to take care of this legislatively."

Under the 1984 Hatch-Waxman Act, makers of generic drugs can begin producing generics before the original drug patent expires by challenging the validity of that drug's patent. Instead of fighting the battle in court, the patent holders often simply pay the generic makers to drop their efforts.

Such was the case when Barr Pharmaceuticals struck a deal to drop its challenge to Bayer's Cipro patent in 1997. With the support of the Federal Trade Commission, a cadre of organizations, including CVS Pharmacy and Rite Aid took the agreement to court, accusing such pay-for-delay deals of violating antitrust laws and unlawfully delaying the distribution of more affordable generics.

On 7 September, a US appeals court in New York may have effectively ended that fight by refusing to reconsider an earlier decision that such deals cannot be denied—in large part because to do so would effectively force companies to pursue litigation. The rational is typically dubbed the "Tamoxifen doctrine," named after a similar 2006 case involving the cancer drug.

The last chance to resolve the issue in the court system would be if the Supreme Court decides to hear the case, but many proponents of outlawing pay-for-delay deals, such as Rutgers Law School antitrust expert Michael Carrier, are skeptical this will happen, largely because the court has refused to hear similar cases in the past, including the Tamoxifen case.

The "Preserve Access to Affordable Generics Act," which would effectively nix pay-for-delay deals, is currently included as part of the Senate's 2011 financial services appropriations bill. Prior to the congressional summer recess, the act narrowly escaped exclusion from the bill by a group of senators who claim that the act would actually inhibit generic drugs by drawing companies into long and legal disputes.

The timeline for the bill's approval is not certain. The act could still be removed before the Senate's vote, which may be delayed until after the midterm elections in November.

Stu Hutson