

A PATCH

OF

Life





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– Dr Suzie Miller

A version of a stick-on patch already in use to offset common jet lag could become one of the most potent weapons against birth complications caused by lack of oxygen.

WORDS Melissa Marino

► A simple melatonin patch – similar to that used by weary international travellers to combat jet lag – may save the lives of millions of babies and prevent countless more from suffering irreparable brain damage.

Melatonin is a powerful antioxidant that researchers have found can neutralise the effects of birth asphyxia, a lack of oxygen caused by complications such as umbilical cord entanglement or obstructed delivery.

Every year, almost four million babies die before they are a month old. Some 1.5 million of these deaths occur in India alone – and more than half are due to asphyxia at birth.

The patch, not much bigger than a bandaid and stuck gently onto a baby's back, could offer a simple, cheap miracle in countries that do not have the luxury of modern maternity and neonatal care.

PHOTO: JAMES BRAUND

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In a hospital such as Melbourne's Monash Medical Centre, doctors would treat five or six cases of birth asphyxia each year from about 4000 births.

For an equivalent-size hospital with 8000 births a year in a city such as Lucknow, in India's poorest state, Uttar Pradesh, that number is more like five or six a week. This is due to a lack of foetal monitoring equipment and the lack of capacity for emergency caesareans if babies get into trouble. Many newborns are also taken to Indian hospitals following birth asphyxia after being born at home.

It is a tragedy on a large scale and has spurred researchers such as Associate Professor Michael Fahey to find an answer. "We've got millions of babies dying every year within their first month of life because they are in a low-resource country," he says.

Associate Professor Fahey, who is head of paediatric neurology at Monash Children's Hospital in Melbourne, is also a clinical research scientist. He has been working with a multidisciplinary team from the Ritchie Centre (at Monash Institute of Medical Research-Prince Henry's Institute and Monash University) on new therapies to improve survival rates and outcomes for babies who have suffered birth asphyxia. One of the potential therapies is the melatonin patch, which researchers are confident will significantly reduce brain damage and fatalities caused by severe lack of oxygen at birth.

The research has advanced to the point that the team hopes to start a pilot study soon with Indian partner hospital King George's Medical Centre in Lucknow.

Alongside that trial are training clinics, already being established in rural areas surrounding Lucknow, where health workers are being taught to recognise birth asphyxia so that melatonin patches can also be used out in the community.

"We've got an opportunity to bring into this setting something that is cheap, easily translatable, stable, safe and doesn't require high technology to make a massive impact both in India and around the world," Associate Professor Fahey says.

Free-radical scavenger

The ability of melatonin to reduce brain damage was first confirmed almost a decade ago by team co-leader Dr Suzie Miller, an international specialist investigating brain development and neuroprotection.

Working with Ritchie Centre deputy director Professor Graham Jenkin and director Professor Euan Wallace, Dr Miller showed for the first time that melatonin, a naturally occurring hormone and powerful antioxidant, was an efficient scavenger within the foetal brain, mopping up dangerous oxygen free radicals that flood the system and cause brain injury after asphyxia.

As babies do not produce melatonin until they are three or four months old, this hormone, which also dictates

A sticky solution

As training to identify asphyxia is rolled out across rural Uttar Pradesh in India, a different challenge awaits King George's Medical Centre in Lucknow, which could soon host the first melatonin patch clinical trials: a supply of reliable patches is required.

"We must provide a patch with a specific concentration of melatonin to be released over a known period," Professor Graham Jenkin says.

Work with UK and German collaborators is nearing completion on the development of a suitable patch, containing uniform levels of melatonin and providing a consistent release rate.

Associate Professor Michael Fahey says the ultimate success of the project will also depend on enlisting local partners to manufacture the patch.

Key in this phase has been Supreet Khosla, who as a Delhi-based Australian Trade Commission business development manager assists Australian businesses to grow internationally and also promotes the transfer of technology and R&D solutions from Australia to India.

Ms Khosla introduced the Monash University team to staff at the Stanford-India Biodesign Center in New Delhi, which teams up doctors and entrepreneurs to develop cost-effective health innovations in India.

Ms Khosla says there is desperate need for such an innovation in India, which has a wide health care divide between rich and poor. "Rural India often gets ignored because all of the private hospitals run in and around cities where people have the ability to pay," she says.

Professor Euan Wallace says that, unlike many medical technologies, the melatonin patch is "dirt cheap". It might cost only one or two Australian dollars to save a life or prevent a lifelong disability.

PHOTOS: ASSOCIATE PROFESSOR MICHAEL FAHEY



Dr Atul Malhotra with villagers from Shivgarh, Uttar Pradesh

These are culturally sensitive communities so you need to gel and work with them before they will accept a therapy that has not been used previously.

– Dr Atul Malhotra

Awaken to free radicals

It would not come as any great surprise to new parents to learn that babies do not produce melatonin – the hormone responsible for a regular sleep–wake cycle – until they are three or four months old. But this biological developmental delay that allows them to feed through the night on a 24-hour cycle when they are very young has a major pitfall besides the sleepless nights it gives parents.

Melatonin is the antidote to chemically reactive molecules (free radicals) formed as a consequence of asphyxia that can damage the structure of cells and cause them to die. For babies who have suffered birth asphyxia this absence of natural melatonin can be potentially deadly.

Oxygen free radicals are a normal part of life. We produce them as we breathe as part of the process of getting energy from oxygen, but Monash University PhD candidate James Aridas explains that when oxygen is returned to a baby after it has experienced asphyxia, it floods the system, creating too many free radicals for the body to remove. Babies who to that point have been reliant on melatonin via their mother in utero have limited in-built defence.

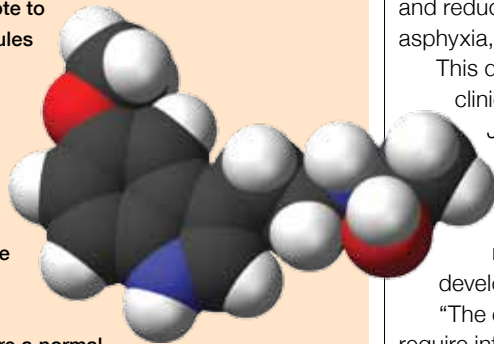
“This is why giving melatonin to babies could make such a dramatic difference,” he says. “The patches would rebalance the system.”

Dream clinic a step closer

The ultimate “dream” for Associate Professor Michael Fahey is to establish a permanent centre for cerebral palsy (which can be caused by birth asphyxia), in Lucknow, India. Extending beyond the scope of the current projects, it would provide ongoing training and education as well as operating as a monitoring facility for babies treated with melatonin and as a therapy centre for children with cerebral palsy. While this is very much a work in progress, and may be some years before it comes to fruition, it has the support of the Australian High Commissioner to India, Patrick Suckling. And so the Ritchie Centre Monash Institute of Medical Research-Prince Henry’s Institute researchers are daring to dream. “We are all hoping that it becomes a dream come true,” Professor Graham Jenkin says.

Ritchie Centre

- The Ritchie Centre is part of the Monash Institute of Medical Research-Prince Henry’s Institute (MIMR-PHI) and is the principal research centre for Monash University’s Departments of Obstetrics and Gynaecology, and Paediatrics.
- It is also the principal research partner of Monash Women’s Services and Monash Children’s Hospital at Monash Health.
- It is located within the Monash Health Translation Precinct at Monash Medical Centre, in Melbourne, Victoria, which is home to the MIMR-PHI Institute, Monash Health and Monash University’s School of Clinical Sciences.
- There are 150 research staff and students, including foetal physiologists, immunologists, stem cell biologists, neonatologists, paediatricians, obstetricians, gynaecologists and radiologists.



Melatonin molecule

our circadian rhythms, needs to be administered if asphyxia has occurred.

Since her initial discovery, Dr Miller and her colleagues have worked to advance those findings and develop them to the point that they can become part of medical practice. Their recent work, proving a patch is effective in delivering melatonin and reducing brain damage following birth asphyxia, has significant implications.

This discovery, proved through pre-clinical research by PhD candidate James Aridas, means that melatonin could be administered cheaply and simply in community settings as well as in hospitals, making it ideal for use in developing countries such as India.

“The exciting thing is that it doesn’t require intensive care,” Dr Miller says. “The melatonin patch doesn’t even need refrigeration. It is literally applied like a bandaid.”

For Dr Miller, it is the fulfilment of a dream: “From 10 years ago to get to a point where it’s almost ready to go in a clinical situation really is amazing.”

India connection

Lucknow is considered an ideal destination for the next advancement of this research, not only because birth asphyxia is a major problem there, but also because of the existence of important research ties.

Dr Atul Malhotra, a neonatal paediatrician at Monash Children’s Hospital and fellow Ritchie Centre team-member, is from India and trained with Dr Vishwajeet Kumar, head of the Lucknow Community Empowerment Lab, who is collaborating to inform patch development and introduce the rural training package.

The Community Empowerment Lab has long-established links with more than 3400 villages around Lucknow, an area that Dr Kumar describes as among the most dangerous in the world for babies and mothers.

The lab works within the community to tackle issues including neonatal and maternal health, often in partnership with international institutions, to help develop low-cost but effective technologies and innovations to lift long-term prospects for people.

Dr Kumar says that a melatonin patch is potentially the single most important innovation developed to reduce deaths from birth asphyxia.

People therefore need to be made familiar with the concept and trained how to use a patch, but it is also crucial that they learn how to recognise birth asphyxia in the first place.

Families in the region often see infant mortality as “fatalistic”, or an inevitable part of life. But deaths could

be prevented if people could identify birth asphyxia symptoms, Dr Kumar says.

“What your mind doesn’t know your eyes don’t see,” he says. “In most cases they don’t realise firstly the early warning signs of a fatal event and secondly that they can actually do something about it.”

Dr Malhotra, a senior lecturer at Monash, Associate Professor Fahey and Professor Jenkin visited Lucknow, developing training materials and guides for health workers. These materials will be distributed throughout the region and ongoing training and monitoring will be conducted with the help of the Community Empowerment Lab and its networks.

First steps

The first six hours after a baby is born with asphyxia are crucial, Dr Malhotra says. “Treatment needs to begin as soon as possible to lessen the consequences, so correct diagnosis is vital. The first step is identifying an infant at risk. The next is to apply the melatonin patch and then head for hospital for further care ... although, of course, it’s not necessarily that simple.”

Applying a melatonin patch out in a community is not just a matter of explaining its medical purpose, but also making it acceptable, he says. A bandaid-style patch might be commonplace in the west, but quite foreign in a small village in Uttar Pradesh.

“These are culturally sensitive communities so you need to gel and work with them before they will accept a therapy that has not been used previously,” he says.

Another example of a simple, but real, obstacle is the practice in some areas to oil newborn babies – something that could interfere with the patch’s ability to stick to the skin and the penetration of melatonin.

“So you can’t just go into a community and say ‘let’s go’. You have to get to know the people. It’s not something you can rush.”

Future growth

The pre-clinical research in Melbourne and training work in India has been funded through the National Health and Medical Research Council and the Bill and Melinda Gates Foundation in an initiative spearheaded by Ritchie Centre director Professor Wallace. Further funding is now being sought for the clinical trials.

“While melatonin as a therapy could be used anywhere, it will be particularly applicable and effective in low-resource settings, such as India or other parts of Asia or Africa,” Professor Wallace says.

“If this is successful, we are going to need to develop a whole suite of training materials in Vietnamese, Khmer, Swahili,” he says. “This is just the starting point.” ■