Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Recycle: Do It for the Kids

AT THIS TIME of coronavirus disease 2019 (COVID-19), in which government agencies, medical professionals, and the general public are calling for an effective treatment, expectations of the pharmaceutical industry are high. Unveiling of a new cure-all magic bullet is, unfortunately, an unrealistic proposition. Vaccines aside, the time and expense of bringing new drugs to market for this specific indication is too great to meet current needs. It is hardly surprising that attention has been drawn to existing drugs, in the hope of finding a cure.

Hydroxychloroquine and chloroquine enjoyed a brief departure from roles in malarial and rheumatic disease management to emerge as the darlings of COVID-19 treatment. In late March of 2020, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) allowing physicians the ability to prescribe these medications to patients with a laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This was largely based on data from 2005, when researchers found that chloroquine is a potent inhibitor of the SARS coronavirus in in vitro primate cell cultures.[1] Hydroxychloroquine quickly gained international attention during the current epidemic, despite evidence from human trials; incredibly, some people started consuming hydroxychloroquine as a prophylactic against SARS-CoV-2 infection. Only weeks later, the US National Institutes of Health warned against this treatment, citing insufficient clinical data to recommend this class of drugs for the treatment of COVID-19, as well as concern about significant and potentially fatal side effects (prolonged QTc interval being the most noteworthy). Investigators have now turned their attention to a host of other antitumor, antimalarial, antibacterial, and antiretroviral medications with activity against SARS-CoV-2 infection, hoping for an effective therapy.

Although this hydroxychloroquine episode has been an unfortunate distraction, "repurposing" of existing drugs for new medical indications is a successful strategy that has gained popularity in recent years. Examples abound in the medical literature. Propranolol, developed as an antihypertensive agent, is also a useful treatment for pediatric hemangiomas and a wide range of malignancies, including angiosarcoma. Thalidomide, withdrawn from clinical use as an antiemetic for pregnancy-related morning sickness, is effective in treating complications of leprosy and is most recently being used to treat patients with multiple myeloma. Flumazenil, used for treatment of patients with benzodiazepine overdose, is used for hypersomnia and emergence delirium in children.[2] Dexamethasone, a long-used steroid, is also an effective anti-emetic but may also play a role in treatment of patients with current SARS-CoV-2 infection.

Given the opportunity, the advantages of repurposing drugs are obvious. Existing drugs that have survived the FDA approval process have known pharmacokinetic and safety profiles. This allows any newly identified use of a previously approved drug to be readily evaluated in phase 2 clinical trials; it also may allow a measure of confidence in using a drug for an "off-label" indication. This is particularly important as research and development costs for pharmaceutical companies are rapidly expanding. The process of screening new therapeutic molecules, conducting preclinical in vitro trials, and then confirming with clinical trials in humans, takes an average of 15 years and $800 million, all to bring only a single drug to market.[3] Moreover, the current pharmaceutical research and development business model is threatened by poor transparency, questions of integrity and ethical practice, constricted healthcare budgets, loss of revenue caused by an increase in availability of generic medications, and a lack of novel therapeutic agents, all leading to fewer new drugs coming to market for clinical use.[4,5]

A medication with a long history of use in adults, with known safety, efficacy, and tolerability data, may be used in children with a greater degree of comfort, especially if toxicity studies in pediatric populations are not yet conducted.[6-8] Such drugs also have efficacy in "off-label" use. Off-label drug use is common in pediatrics, as the vigorous studies needed to obtain FDA approval are not conducted in children; case reports and case series of off-label use aid physicians in increasing the number of pharmacologic therapies in the armamentarium.

Drug repurposing, therefore, is 1 solution to the "productivity gap" that plagues the pharmaceutical industry. In this issue of the *Journal of Cardiothoracic and Vascular*

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Anesthesia, Charlton et al. described the use of labetalol in the management of paradoxical hypertension after aortic coarctation repair in children.[9] Labetalol is not a new medication; it was discovered in 1966 and first licensed for medical practice in 1977. Although safety and efficacy studies for labetalol have not been performed in pediatric patients, this drug has been and is used successfully in this population. Its use in the management of patients with paradoxical hypertension was initially described in 1988, but other, newer drugs eventually surpassed labetalol in clinical use—notably, nitroprusside and angiotensin-converting enzyme inhibitors, particularly for immediate blood pressure control after coarctation repair.[10,11] More recently, dexmedetomidine, a wonder drug of pediatric anesthesiology that seems to fix everything, has, too, been cited as an adjunct to assist in paradoxical hypertension.[12]

When considering the anesthesia required for repair of complex congenital heart defects, providing anesthesia for repair of aortic coarctation seems much simpler. However, anesthesiologists have a critical role in establishing early control of postoperative hypertension in this population. Adequate treatment of hypertension and selection of appropriate agents after coarctation repair are important to prevent stroke, hemorrhage, and mesenteric arteritis, among other complications.[13] The authors of this study of labetalol provided an opportunity for us to reconsider paradoxical hypertension after coarctation repair, an important clinical issue that all pediatric cardiac anesthesiologists and intensivists encounter at some point.

Indeed, anesthesiologists are familiar with immediate hypertension that occurs during repair of the coarctation, even in the absence of a residual gradient across the aortic arch. However, this hypertension persists up to several days after coarctation repair. The mechanism of action for postoperative paradoxical hypertension is 2-pronged. The initial elevation is caused by higher baroreceptor setpoints—baroreceptors sense relative "hypotension" after relief of the obstruction and instigate an increase in norepinephrine levels to restore blood pressure. The second phase of hypertension is caused by renin-angiotensin-aldosterone system activation, with elevated plasma renin activity in the first postoperative week.[11] Beta-adrenergic antagonists are effective to decrease plasma renin activity but may require concomitant use of vasodilators to achieve blood pressure goals. It is here that labetalol enjoys an advantage—as both an alpha- and beta-adrenergic antagonist, it decreases norepinephrine concentrations and activation of the renin-angiotensin-aldosterone system.[9] Charlton et al. stated that some children in their study required nitroprusside in addition to labetalol but hypothesized that higher doses of labetalol may have eliminated this need.

Charlton et al. have brought back into focus an old medication, labetalol, that is uniquely situated to manage patients with paradoxical hypertension; their study also confirmed increased renin activity as a cause of persistent hypertension after repair of aortic coarctation. The use of an older drug, with activity against both alpha- and beta-adrenergic receptors, highlights that repurposing drugs is particularly helpful for pediatric use.

In summary, this serves as a reminder that old medications can still be highly effective and perfect for the problem at hand. When thoughtfully studied and used for the intended purpose or repurposed for a new indication, medicines that have long been in our pharmaceutical armory can continue to be useful.

Conflict of Interest

None.

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