Exploring how kidney failure impacts the body's systems

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Brad Urquhart, a Schulich School of Medicine & Dentistry professor (Physiology & Pharmacology), is exploring the processes that govern the response to drugs in kidney failure.

For the 35,000 Canadians currently on kidney dialysis, several medications – up to a dozen in some cases – are prescribed to control such things as diabetes, hypertension and various types of infection.

But how is the body reacting to these drug cocktails, and are the right

combinations and doses being optimized by physicians? This is where Brad Urquhart comes in.

Whenever a drug is prescribed, it is meant to do something beneficial, and not remain in the bloodstream permanently. But when kidneys start to fail, drugs aren't eliminated in the urine; they linger in the body.

"You can imagine when you give a drug to a patient, we work hard getting a certain level of the drug in the blood to have a beneficial effect for each patient," said Urquhart, a Schulich School of Medicine & Dentistry professor (Physiology & Pharmacology). "Too much will have harmful effects, too little and there is no benefit."

Now, Urquhart has discovered the failure of one organ does not bode well for another. His research shows the metabolism of drugs through the liver is decreased in people with kidney disease. This is of interest, since 70 per cent of the drugs given to individuals with kidney disease are metabolized by the liver.

"We're specifically looking at what changes in the liver when the kidney fails," he said. "It doesn't make sense that when the kidney fails, the liver is also affected. Why is liver function impacted and what impact does that have on a patient's medication?"

In partnership, the liver and kidneys serve as the body's main filters of the bloodstream. Medications travel through the liver first. There, they are broken down and shipped throughout the body via the bloodstream. The bloodstream is then filtered by the kidneys and waste – from toxins to unused portions of medication – is removed in the urine.

Urquhart's findings are counterintuitive, certainly. When one organ fails (the kidneys), another (the liver) often works harder to compensate.

"What we're finding is it's actually the opposite," he said.

Although the effect of kidney failure on the renal excretion of drugs is well documented, evidence suggests absorption, distribution and metabolism of many drugs are significantly altered, leading to variable efficacy results. Urquhart is trying to gain a better understanding of the processes that manage the response to drugs in kidney failure.

While not focusing on a specific drug, Urquhart is looking at the specific pathways impacting 50 per cent of the drugs taken by kidney patients.

"The real thing that will help patient care is if we find out what the changes are in the different pathways," Urquhart said. "(The goal is for a doctor to know) that if you're on a drug that is metabolized by this pathway – and we know that pathway is altered in patients with kidney diseases – then they could alter the dose of the drug or even the drug itself."

While the liver is the major site of metabolism in the body, drugs can be metabolized by a number of different pathways.

Some of these pathways are down in kidney disease; some aren't, Urquhart said. Identifying which is key, as dialysis patients take anywhere from 7-12 drugs. Their chance of suffering from adverse medication events is almost three times greater than the rest of the population.

"We're always going to need the drugs for this. But putting all these drugs in our body, patients have a higher incidence of hospitalization because of adverse events. So, it's about getting that number down and increasing their quality of life," Urquhart said. "We want to prevent patients from having toxic reactions to drugs. … But there is no point having patients take all these drugs if they're not having a beneficial

effect."

Two recent grants received by Urquhart (Canadian Institutes for Health Research and the Canadian Foundation for Innovation) will drive his research, including the purchase of a mass spectrometer, allowing him to study, at a very sensitive level, the masses and relative concentrations of atoms and molecules.

With the number of Canadians on dialysis expected to double over the next decade, Urquhart anticipates better results for these patients in managing their drug therapy.

"It about giving them back that quality of life they deserve," he said.

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