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Diuretic-resistant fluid overload

Fluid overload is a frequent complication of many severe diseases, including advanced liver and kidney disease, heart failure and cancer. Diuretics are the mainstay of therapy for fluid overload but in many patients, they stop being effective and patients become diuretic-resistant over time. Diuretic resistance is common and other treatment options are generally limited. We are developing the alfapump platform as a potential chronic treatment solution for these patients with diuretic-resistant fluid overload.

What are diuretics?

HOW DO DIURETICS WORK?

- Most diuretics inhibit the re-absorption of sodium from primary urine in the renal tubular system leading to increased sodium excretion (natriuresis) and water excretion (diuresis). There are different classes of diuretics which act at different renal segments. Blocking one segment can alter the sodium re-absorption at another segment and therefore a combination of different diuretics is sometimes required.
- Loop diuretics are the most powerful diuretics, inhibiting the sodium re-absorption in the loop of Henle, which is responsible for re-absorption of ~25% of the urine sodium load.

CHARACTERISTICS

- Bioavailability of diuretics is highly variable: absorption of diuretics and diuretic delivery are variable amongst patients leading to different diuretic responses.
- Loop diuretics are short-acting drugs: most diuresis occurs over the first few hours after administration.

What is Diuretic Resistance?

Diuretic Resistance (DR) is the condition where patients fail to decongest despite adequate and escalating doses of diuretics. In other words, diuretics fail to control the salt and water excretion even when used in appropriate doses.

CAUSES OF DIURETIC RESISTANCE

- **Pharmacokinetic changes:** a decrease in renal function can cause a reduced rate of diuretic drug response leading to delay in time to achieve peak concentrations
- **Pharmacodynamic changes:** drug-drug interactions can cause reduced sodium and/or water excretion
- **'Diuretic braking' phenomenon:** repeated diuretic dosing can cause augmented sodium re-absorption and diminished natriuresis, shifting the dose-response curve (i.e., higher doses required to achieve same diuretic effect)
- **Post-diuretic sodium retention:** short-acting effect and an inappropriate salt diet can cause sodium retention after diuretic treatment
- **Pharmacogenetics** may also play a role

MANAGEMENT OF DIURETIC RESISTANCE

- Increase dose to overcome reduced absorption of diuretics
- Increase frequency of diuretics to overcome post-diuretic sodium retention. Studies have shown that continuous vs bolus administration caused rapid development of DR
- Change route of administration from oral to IV
- Combine different diuretics for synergistic effect and to prevent re-absorption of sodium at another renal segment
- Strict salt diet

None of these strategies have proven to be very effective.

Diuretic resistance is a major cause of recurrent hospitalisations in patients with chronic heart failure and presents a heavy burden on hospitals & patients leading to prolonged hospital stay and to an increase in mortality.

$13bn

Annual costs of U.S. HF-related hospitalisation

90%

HF-related hospitalisations due to fluid overload

20-50%

hospitalised patients with a poor initial response to IV loop diuretics

50%

patients leaving the hospital with residual congestion

1 in 4

patients re-admitted to hospital within 30 days

Sources: Ravan et al., 2002; Gupta et al., 2019; Shah et al., 2017; cvpharmacology.com