Furosemide: Properties, Alternatives, and the Medication Approval Process

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Pre-hospital treatment of critical patients is a key factor in determining overall outcomes. Actions that are completed in the field can vastly improve patient wellness during their hospital stay and after discharge. However, there is more to treating a patient than simply pushing medications through an IV in their peripheral vein. Certain medications are indicated for specific conditions and of these, some work better than others. For edema, the common medication is furosemide, although this is not the only drug that can treat edema in the pre-hospital or hospital settings. Thiazides, thiazide-like diuretics, and potassium-sparing diuretics are also useful treatments and will be discussed later.

Furosemide

Furosemide (Lasix) is a potent loop diuretic that is used to increase urine production to reduce fluid in the body. It is commonly referred to as a “water pill” or “fluid pill” due to its effects (Guy, 2011, p201). Loop diuretics are specifically used for edema from heart failure, hypertension, and as an adjunctive treatment in acute pulmonary edema (Comerford, 2016; Guy, 2011; Levy and Bellou, 2013; Vasco et al, 2016; Pacifici, 2013). It acts by inhibiting sodium and chloride reabsorption in the ascending loop of Henle, which in turn increases urine output (Guy, 2011; Comerford, 2016; Pacifici, 2013). It also increases the excretion of potassium, similar to thiazide diuretics (Comerford, 2016) and decreasing water absorption in the kidneys (Guy, 2011). Furosemide binds exclusively to plasma proteins and bilirubin displacement is negligible when using normal doses. It enters the tubules by tubular secretion and not filtration. While it can be used in pediatric patients, the pharmacokinetics are driven by the maturity of the kidneys (Pacifici, 2013). The long-term use of furosemide is associated with low bone density as a result of its mechanism of action, which is promotion of calcium wasting (Vasco et al, 2016).

Other loop diuretics include bumetadine, ethacrynic sodium, and torsemide. Like thiazide diuretics, loop diuretics increase excretion of potassium, although they do produce more diuresis and electrolyte loss than thiazide diuretics (Vasco et al, 2016). While diuretics are very effective, they are not without consequence. Side effects include dizziness, weakness, electrolyte imbalances, hearing loss and tinnitus, hypovolemia, and cardiovascular collapse (Guy, 2011; Comerford, 2016). When treating heart failure and pulmonary edema, loop diuretics are more effective than other diuretics (Guy, 2011). However, research has shown that they may escalate bone metabolic disease (Vasco et al, 2016). Thiazides and thiazide-like diuretics lack these effects, and research suggests that they can produce a protective effect on bone density (Vasco et al, 2016). Loop diuretics initially cause vasodilation but often have a latent vasoconstriction phase as well (Levy and Bellou, 2013). Resistance to loop diuretics has been noted and patients with resistance typically have poorer outcomes while treating acute heart failure. Patients with renal failure have been noted to have worsening diagnosis as a result of receiving loop diuretics (Levy and Bellou, 2013).

Alternatives to Loop Diuretics

Furosemide is very common in the pre-hospital and hospital setting, although there are other drugs that can be utilized. These include thiazide and thiazide-like diuretics, and potassium-sparing diuretics. Thiazide and thiazide-like diuretics include HCTZ, indapamide, metolazone. These drugs “interfere with sodium transport across the tubules of the cortical diluting segment in the nephron, thereby increasing renal excretion of sodium, chloride, water, and potassium and decreasing calcium excretion” (Comerford, 2016, p49). These drugs also

exhibit and antihypertensive effect, although the exact mechanism is unknown (Comerford, 2016). Recent studies have indicated that thiazides can exert a renal protective action when in combination with ACE inhibitors or AT-1 receptor blockers in patients with chronic kidney disease (Vasco et al, 2016). Loop diuretics have only partially exhibited these effects. Potassium-sparing diuretics include amiloride hydrochloride, spironolactone, triamterene (Comerford, 2016). Spironolactone specifically “inhibits aldosterone at the distal renal tubules, also promoting sodium excretion and potassium retention” (Comerford, 2016, p48).

Medication Approval Process

The process for medication approval in humans is long and somewhat complex. According to the FDA, the process begins when an investigational new drug application is submitted from a sponsor (company, research institution, or other organization) that shows prior research and testing in animals (2017). A review board consisting of scientists, hospitals, and research institutions along with the FDA decide if a drug is safe enough to begin human trials (Review, 2017). The board then develops and approves protocols for testing which include the type of people that can be included in the trial, schedule of testing and procedures, medication dosage, the length of study, overall objectives, and many more details (Review, 2017). In addition to the pre-trial details, the board must also ensure that the patients understand the risks and do not cause harm to the patients (Review, 2017). The first phase of testing is administered to a small group of healthy volunteers to determine side effects, metabolism, and excretion (Review, 2017). The second phase is conducted on patients with a particular disease to determine its effectiveness against a different drug or placebo (Review, 2017). Next is a large-scale trial, with several thousand patients (Review, 2017). After clinical trials are complete, the company

can submit a new drug application to the FDA for consideration (Review, 2017). If approved, the company can begin manufacturing and marketing the new drug to the public (Review, 2017). Even after the drug is manufactured, it will be continuously studied to determine its effectiveness and any other side effects it may cause (Review, 2017). Loop diuretics were developed in the 1960s (Pacifici, 2013).

Off-Label Use of Medications

Just because the FDA has approved a drug for a specific purpose does not mean that it will always be used for it. The companies that approve medications also monitor for off-label use of the medication, which is the "unapproved use of an approved medication," according to the FDA (Label, 2017). This can include use for a condition it is not approved to treat, dispensed in a different way from its original manufacture, or is given in a different dose (Label, 2017). However, they do advise consumers to speak with their doctors as they can prescribe it if it is medically necessary or if they believe that the benefits outweigh the risks (Label, 2017).

Conclusion

Loop diuretics, thiazide and thiazide-like diuretics, and potassium-sparing diuretics are all useful medications to treat edema in the pre-hospital and hospital settings. Each have their benefits and risks, which are carefully evaluated by the person administering the medication to the patient. This evaluation uses the information that is gleaned from clinicals trials carried out by the FDA and presented to medical personnel to treat their patients who present with edema. Caution is always used with them as there is always a potential to cause adverse effects to the

patient, even when least expected. The benefit to the patient should always outweigh the risks of administering a medication to improve out-of-hospital outcomes for the patient.

References

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