Loop diuretics dose response curve and dosing dosing interval

Loop diuretics (furosemide and bumetanide) are the most potent of the diuretics and are widely used in the treatment of pulmonary and systemic edema. Loop diuretics bind reversibly to a chloride channel receptor site in the ascending limb of the loop of Henle, inhibiting the reabsorption of filtered sodium and chloride. This reduces the hypertonicity of the renal medulla, inhibiting water reabsorption by the collecting ducts. In addition, loop diuretics increase the excretion of potassium, hydrogen ions, magnesium, and calcium. Both furosemide and bumetanide are available in oral and intravenous preparations. Following an intravenous dose of either agent, diuresis is very rapid, beginning 15 minutes after administration and lasting up to 2 hours. Following an oral dose, diuresis begins in 30 to 60 minutes and lasts 2 to 4 hours. The oral bioavailability of furosemide is 60% and is 100% for bumetanide. Loop diuretics are effective in renal failure, but higher doses are required. However, the elimination of furosemide and, to a lesser extent, bumetanide is impaired in renal failure, increasing the risk of side effects. The half-life of furosemide is prolonged in advanced renal dysfunction, and the half-life of torsemide is doubled in hepatic dysfunction. By inhibiting NaCl reabsorption in the water-impermeable thick ascending limb of Henle loop, loop diuretics interfere with both the diluting and the concentrating mechanism. Loop diuretics are also the drugs of choice for the treatment of. in those not treated with a loop diuretic and– 9.4 ± 10 mL/min/1.73 m 2. sodium-potassium-2 chloride (Na + /K + /2Cl–) symporter on the luminal border of the thick ascending limb of the loop of Henle. Loop diuretics also have a ceiling dose. This is the dose that shows the maximum fractional sodium excretion. Doses higher than the ceiling dose start to yield diminishing returns and are only slightly more effective. Increasing the frequency of dosing with the ceiling dose is more effective than increasing the dose of furosemide. Loop diuretics have a sigmoidal dose-responsive effect. Doses smaller than the threshold dose produce little or no diuretic effect. It takes increasing sizes of doses until diuresis occurs. That's the threshold dose. Although the loop diuretics are acidic, they vary in their structure. Nonetheless, they all act by inhibiting the. excretion; and a brief increase followed by a more prolonged decrease in uric acid excretion. Loop diuretics also stimulate renal prostaglandin synthesis, particularly that of the vasodilatory prostaglandin E 2 (PGE 2). Angiotensin-II generated following the administration of intravenous loop diuretics and increased synthesis of PGE 2. The main adverse effect of loop diuretics is an excessive clinical effect: hypovolemia, hypokalemia, hypochloremic metabolic alkalosis, and hypomagnesemia. Other side effects include deafness, hyperuricemia (and gout), and allergic skin rashes. The effect of loop diuretics on serum sodium concentration is difficult to predict. The urinary sodium concentration in a patient on a furosemide infusion is typically less than 100 mmol/l; thus, acutely, hypernatremia can occur. However, if urinary losses are replaced with a low-sodium solution (e.g., intravenous 5% dextrose or oral water), hyponatremia will develop. Chronic furosemide use typically results in hyponatremia. Furosemide and, to a lesser extent, bumetanide can cause deafness. This risk is greatest in patients with renal impairment who are receiving high doses of furosemide, by either infusion or rapidly administered intravenous bolus doses. The role of loop diuretics in the treatment of systemic edema and renal failure is debatable and is discussed in. Article in classic view ePub (beta) PDF (536K) Citation. excretion by more than 60%, also by diminishing voltage-dependent paracellular transport. Uniquely, furosemide also has a venodilatory action mediated by an endothelium-dependent hyperpolarizing action that can acutely lower central filling pressures in the setting of congestive heart failure (CHF). The total

renal blood flow is maintained or increased, and the glomerular filtration rate (GFR) is little changed during administration of loop diuretics to normal subjects, although there is marked redistribution of blood flow from the inner to the outer cortex. Furosemide increases the renal generation of prostaglandins (PGs); blockade of cyclooxygenase (COX) prevents furosemide-induced renal vasodilatation. Loop diuretics stimulate renin secretion, both acute and chronic, partly from ECV depletion, but also from direct effects on the macula densa. The ePub format is best viewed in the iBooks reader. You may notice problems with. Haschek and Rousseaux's Handbook of Toxicologic Pathology (Third Edition), 2013. Loop diuretics, also known as high ceiling or high efficacy. treat hypercalcemia. As discussed earlier (see Fig. 22-6), loop diuretics decrease Ca 2+ reabsorption in the TALH. In patients with hypercalcemia, furosemide is given intravenously, which produces a prompt reduction in plasma Ca 2+ concentration. To maintain plasma volume and prevent Na + and K + wasting, normal saline must be infused simultaneously at a rate that matches urine flow. Loop diuretics such as furosemide, ethacrynic acid, and bumetadine (i.e., those with primary action on the loop of Henle in the TEENney) produce rapid, acute, but reversible auditory changes. A common clinical complaint is tinnitus, but there are also notable threshold shifts for sound sensation across all frequencies. The stria vascularis is notably edematous; characteristic features include swelling of marginal cells, shrinkage of intermediate cells, and dilation of the intercellular spaces rapidly following intravenous dosing. The loop diuretics directly affect the stria vascularis from the vasculature, resulting in rapid onset. The edema is due to inhibition of ion transport by Na + /K + -ATPases at the basolateral membranes of marginal cells, resulting in osmotic expansion of those cells and the intercellular spaces. The toxicologic mechanism of hearing loss related to loop diuretics is due to attenuation of the endocochlear potential and not to injury of the hair cells. Macrolide antibiotics, such as erythromycin, produce similar but less severe changes. The mechanism for erythromycin's effects has not been elucidated. Oh SW, Han SY. Loop Diuretics in Clinical Practice. Electrolytes & Blood Pressure : E & BP. 2015;13(1):17-21. Study Participants Patients with history of chronic HF were eligible for enrollment into the trial if they were within 24 hours of hospital admission with acute decompensated HF. diuretics, are important drugs for the treatment of several disorders. They have a higher capacity for diuresis compared to other diuretics because they act at the level of the thick ascending limb of the loop of Henle, where 20–25% of the sodium that is filtered through the glomerulus is reabsorbed. This is in contrast to the distal tubule, where 5–10% of the filtered sodium is reabsorbed, and the cortical collecting duct where 1–5% of the filtered sodium is reabsorbed. Fig. 1. Structures of four loop diuretics, available in the United States. Pharmacology and Therapeutics for Dentistry (Seventh Edition), 2017. diuretic efficiency, diuretic resistance, diuretics, acute heart failure. 1 Department of Internal Medicine, Yale University School of Medicine, New Haven, CT Find articles by Jeffrey M. Turner. 2 Program of Applied Translational Research, Yale University School of Medicine, New Haven, CT Find articles by Chirag R. Parikh. The study was approved or determined to qualify as exempt from Institutional Review Board review by the Hospital of the University of Pennsylvania and Yale University Institutional Review Boards. This article has been cited by other articles in PMC. However, the dose of loop diuretic prescribed captures much more than simply the amount of diuretic resistance since dose selection is influenced by factors such as perceived disease severity, degree of congestion, and the physician's individual practices regarding diuretic dosing. In fact, some studies have actually found a lack of survival disadvantage or even a survival benefit associated with higher loop diuretic doses after accounting for these potential confounding factors; illustrating that diuretic dose is not an ideal surrogate for diuretic resistance. 6– 9. For loop diuretics, the response is a function of the amount of drug excreted by the TEENneys. Because of that, you need a larger dose in patients with renal insufficiency or CHF.

Worsening renal function (WRF) was defined as a≥ 20% decrease in eGFR at any time during the hospitalization, unless otherwise specified. 15– 20. The half-life of the various loop diuretics are not the same: 1-1.5 hours for furosemide and 3-4 hours for torsemide. Introduction Diuretics are commonly used to control edema in a number of clinical fields. Diuretics reduce sodium(Na +) reabsorption in specific renal tubules, resulting in an increase in urinary sodium and water excretion. The thick ascending limb of the loop of Henle reabsorbs about 25% of the Na + of the glomerular filtrate. The distal convoluted tubule reabsorbs approximately 5% of the Na + through a thiazide-sensitive sodium-chloride (Na + -Cl -) co-transporter. About 1-2% of the Na + is transported at the distal segment of the distal convoluted tubule and the collecting duct. Loop diuretics can inhibit the largest amount of Na + reabsorption by acting on the thick ascending limb of the loop of Henle. Furosemide inhibits the sodium-potassium-chloride (Na + -K + -2Cl -) co-transporter in the apical membrane of tubular epithelial cells in the thick ascending limb 1). In this article, we review five important aspects of loop diuretics that we must be aware of when we prescribe this medicine: (1) oral versus intravenous treatment, (2) dosage, (3) continuous versus bolus infusion, (4) application in chronic TEENney disease (CKD) patients, and (5) side effects. Penn Cohort We reviewed the charts of all patients with a primary discharge diagnosis of congestive heart failure who had been admitted to non-interventional cardiology and internal medicine services at the Hospital of the University of Pennsylvania within the years of 2004 to 2009. Inclusion required a B-type natriuretic peptide (BNP) level of > 100 pg/mL within 24 hours of admission, receipt of intravenous loop diuretics, and availability of data on fluid intake and output during the hospitalization. In order to focus primarily on the physiology and timing of decongestion, patients with a length of stay≤ 2 days (who likely underwent limited decongestion) and patients with length of stay > 14 days (who likely had either atypical degrees of congestion or non-diuresis-related problems driving the length of stay) were excluded from the cohort. Patients receiving renal replacement therapy were also excluded. In the event of multiple hospitalizations for a single patient, only the first admission meeting the above inclusion criteria was retained. Please see Supplementary Figure 1A for additional details on patient selection. All-cause mortality was determined via the Social Security Death Index and status was ascertained 2.5 years after discharge of the last patient in the dataset. 10. Sang Youb Han Department of Internal Medicine, Inje University College of Medicine, Goyang, Korea. Find articles by Sang Youb Han. Loop diuretic doses were converted to furosemide equivalents with 1 mg bumetanide = 20 mg torsemide = 80 mg furosemide for oral diuretics, and 1 mg bumetanide = 20 mg torsemide = 40 mg furosemide for intravenous diuretics. 21, 22. Methods and Results We independently analyzed two cohorts: 1) consecutive admissions at the University of Pennsylvania (Penn) with a primary discharge diagnosis of HF (n=657) and 2) patients in the ESCAPE dataset (n=390). DE was estimated as the net fluid output produced per 40 mg of furosemide equivalents, then dichotomized into high vs. low DE based on the median value. There was only a moderate correlation between DE and both the IV diuretic dose and net fluid output (r 2≤ 0.26 for all comparisons), indicating that the diuretic efficiency was describing unique information. With the exception of metrics of renal function and pre-admission diuretic therapy, traditional baseline characteristics including right heart catheterization variables were not consistently associated with DE. Low DE was associated with worsened survival even after adjusting for in-hospital diuretic dose, fluid output, in addition to baseline characteristics (Penn HR=1.36, 95% CI 1.04–1.78, p=0.02; ESCAPE HR= 2.86, 95% CI 1.53–5.36, p=0.001. Loop diuretics have a sigmoidal dose-responsive effect. Doses smaller than the threshold dose produce little or no diuretic effect. It takes increasing sizes of doses until diuresis occurs. That's the threshold dose. Conclusions Although in need of validation in less selected populations, low diuretic efficiency during decongestive therapy portends poorer long-term outcomes above and beyond traditional

prognostic factors in patients hospitalized with decompensated heart failure. The half-life of furosemide is prolonged in advanced renal dysfunction, and the half-life of torsemide is doubled in hepatic dysfunction. 4 Section of Heart Failure and Cardiac Transplantation, the Cleveland Clinic, Cleveland, OH Correspondence to Jeffrey M. Testani, MD, MTR, Yale University, 60 Temple Street, Suite 6C, New Haven, CT 06510, Tel: (215) 459-3709, Fax: (203) 746-8373, Diuretics are commonly used to control edema across various clinical fields. Diuretics inhibit sodium reabsorption in specific renal tubules, resulting in increased urinary sodium and water excretion. Loop diuretics are the most potent diuretics. In this article, we review five important aspects of loop diuretics, in particular furosemide, which must be considered when prescribing this medicine: (1) oral versus intravenous treatment, (2) dosage, (3) continuous versus bolus infusion, (4) application in chronic TEENney disease patients, and (5) side effects. The bioavailability of furosemide differs between oral and intravenous therapy. Additionally, the threshold and ceiling doses of furosemide differ according to the particular clinical condition of the patient, for example in patients with severe edema or chronic TEENney disease. To maximize the efficiency of furosemide, a clear understanding of how the mode of delivery will impact bioavailability and the required dosage is necessary. Oh SW, Han SY. Loop Diuretics in Clinical Practice. Electrolytes & Blood Pressure : E & BP. 2015;13(1):17-21. ESCAPE Cohort The ESCAPE Trial was a National Heart, Lung and Blood Institute sponsored, randomized, multicenter trial of therapy guided by pulmonary artery catheter vs. clinical assessment in hospitalized patients with ADHF. Methods and results have been published previously. 11, 12. Department of Internal Medicine, Inje University College of Medicine, Goyang, Korea. Nervous System: Paresthesia, confusion, visual impairment, loss of appetite. heart failure, hepatic cirrhosis, or renal disease treated with DEMADEX at doses higher than those studied in United States antihypertensive trials,. There was no effect of age or sex on the incidence of adverse reactions. There was no fetotoxicity or teratogenicity in rats treated with up to 5 mg/kg/day of torsemide (on a mg/kg basis, this is 15 times a human dose of 20 mg/day; on a mg/m 2 basis, the animal dose is 10 times the human dose), or in rabbits, treated with 1.6 mg/kg/day (on a mg/kg basis, 5 times the human dose of 20 mg/kg/day; on a mg/m 2 basis, 1.7 times this dose). Fetal and maternal toxicity (decrease in average body weight, increase in fetal resorption and delayed fetal ossification) occurred in rabbits and rats given doses 4 (rabbits) and 5 (rats) times larger. The antihypertensive effects of DEMADEX are on the average greater in black patients than in nonblack patients [see. Demadex can be used alone or in combination with other antihypertensive agents. Demadex is contraindicated in patients with hepatic coma. Torsemide is a substrate of CYP2C9. Concomitant use of CYP2C9 inhibitors (e.g., amiodarone, fluconazole, miconazole, oxandrolone) can decrease torsemide clearance and increase torsemide plasma concentrations. Concomitant use of CYP2C9 inducers (e.g., rifampin) increase torsemide clearance and decrease plasma torsemide concentrations. Monitor diuretic effect and blood pressure when used in combination with CYP2C9 inhibitor or inducer. Adjust torsemide dose if necessary. Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and torsemide has been associated with the development of acute renal failure. The antihypertensive and diuretic effects of Demadex can be reduced by NSAIDs. nephrotoxic drugs (e.g., aminoglycosides, cisplatin, and NSAIDs). Monitor volume status and renal function periodically. Concomitant use of Torsemide and cholestyramine has not been studied in humans but, in a study in animals, coadministration of cholestyramine decreased the absorption of orally administered Torsemide. If Torsemide and cholestyramine should be coadministered, administer Torsemide at least one hour before or 4 to 6 h after cholestyramine administration. The following adverse reactions have been identified during the post-approval use of Demadex. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to

estimate their frequency reliably or establish a causal relationship to drug exposure. The recommended initial dose is 5 mg once daily. If the 5 mg dose does not provide adequate reduction in blood pressure within 4 to 6 weeks, increase to 10 mg once daily. If the response to 10 mg is insufficient, add another antihypertensive agent to the treatment regimen. Because Demadex and salicylates compete for secretion by renal tubules, patients receiving high doses of salicylates may experience salicylate toxicity when Demadex is concomitantly administered. Concomitant use with DEMEDEX may increase risk of hypokalemia. There are no data regarding the presence of DEMADEX in human milk or the effects of DEMADEX on the breastfed TEEN. Diuretics can suppress lactation. Impact of pH on O2 delivery to tissue. The recommended initial dose is 5 mg or 10 mg oral Demadex once daily, administered together with an aldosterone antagonist or a potassium-sparing diuretic. If the diuretic response is inadequate, titrate upward by approximately doubling until the desired diuretic response is obtained. Doses higher than 40 mg have not been adequately studied in this population. Hypotension and Worsening Renal Function [see Warnings and Precautions (5.1)]. hypokalemia was observed with greater frequency, in a dose-related manner. DEMADEX can cause potentially symptomatic hypokalemia, hyponatremia, hypomagnesemia, hypocalcemia, and hypochloremic alkalosis. Treatment with DEMADEX can cause an increase in blood glucose levels and hyperglycemia. 4.7 Effects on ability to drive and use machines.

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