May 1, 2014

The New Cardiac Drugs: Emerging Trends and Novel Medications for Cardiovascular Emergencies

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Cardiovascular emergencies account for some of the most common and immediately life-threatening conditions for which patients seek medical care. It is estimated that they are responsible for over 6 million hospitalizations and 800,000 fatalities per year in the US.[1] A significant percentage of active medical research is consequently dedicated to improving both the emergent and long-term management of these conditions. While trying to keep tabs on the growing body of relevant literature is a daunting task, the practicing emergency physician should maintain a basic familiarity with the emerging agents and their evolving use in medical practice. The goals of this article will be to identify some of the more promising of these drugs, describe the literature that supports and defines their use, and explore some of the encouraging trends for future clinical research.

ATRIAL FIBRILLATION AND THE NEW ANTI-DYSRHYTHMICS

Atrial fibrillation (AF) is the most commonly encountered sustained cardiac dysrhythmia, affecting up to 1% of the US population and accounting for over 500K ED visits annually in the US.[1] As our population continues to age, conservative projections estimate an AF prevalence of nearly 15 million patients by the year 2050. At some point during their clinical course, roughly 70% of these individuals will exhibit symptoms ranging from intermittent palpitations and impaired exercise tolerance to significant

thromboembolic complications and outright cardiogenic shock[1]. As the vast majority of patients fall towards the more benign end of this spectrum, the medical community has developed an almost complacent approach to both the acute and long-term management of AF. This is a true disservice though, as chronic AF, regardless of symptoms, has been shown to double patient mortality and increase the individual risk for CVA by 6-fold.[2]

The classic approach to managing AF has focused upon both directly treating the dysrhythmia and also addressing the patient's risk for secondary thromboembolic complications. Therapeutic options have been historically divided into strategies that control the ventricular response to AF and strategies that attempt to convert AF back into normal sinus rhythm (NSR). Most of the debate surrounding the preferred of the two approaches was silenced by the publication of the AFFIRM Trial in 2002. This study featured over 4000 patients with chronic AF who were randomized to either rate control or rhythm control strategies.[3] Although the initial results failed to demonstrate a significant difference in survivability between the two cohorts, a statistically significant reduction in both hospitalization rates and adverse side effects was seen in the rate control group. Of note, this data was published in an environment where practitioners were already more comfortable with the use of rate control agents, namely Class II and Class IV agents, and relatively hesitant to employ rhythm controlling agents, namely Class I and Class III agents.

That said, the past few years have seen a renewed interest in the appropriate role of rhythm control agents. Several recent studies have suggested that chronic AF patients managed via a rhythm control strategy exhibit fewer overall symptoms and improved exercise tolerances, both of which are presumed to translate into an improved quality of life.[4,5,6] Furthermore, a post-hoc analysis of the AFFIRM trial, controlling for those subjects who actually achieved NSR vs. the original intention-to-treat group, demonstrated a significant improvement in survivability in those patients maintained in NSR.[7] As the outcomes of the original AFFIRM trial were analyzed in the intention-to-treat format, one can postulate that the adverse side effects from the rhythm control agents available at the time of the trial most likely led to the resulting failure to demonstrate any cumulative benefit for this strategy.

From an EM perspective, the development of a reliable rhythm control strategy could eliminate thousands of AF-related admissions on an annual basis. The associated savings in health care dollars could easily translate into the tens of millions per year. So why has the medical community been so hesitant to adopt aggressive rhythm control strategies? The bottom line is that the rhythm control agents used in the aforementioned studies were fraught with far too many serious side effects to justify their routine use. They frequently induce systemic hypotension and many exhibit pro-dysrhythmic effects. In addition, many of these agents feature significant extra-cardiac side effects including pulmonary, neurological, and endocrine dysfunction. Finally and most importantly, they all too often don't work, and when successful for converting AF, rarely do so within a narrow enough timeframe to alter the outcomes or disposition of patients in the ED. What we need are safer and more effective options for practical rhythm control. Fortunately there are several promising agents in development that may fill this role. However, to fully understand these agents and their use, one must first own a basic understanding of the pathophysiology behind the evolution of AF.

Available research has firmly established that AF is a progressive condition. The notion that AF begets AF was proposed nearly 20 years ago, and subsequent physiological and clinical studies support this concept.[8] In fact, AF has been shown to induce significant structural and electrical remodeling of the atria within 24 hours of onset, changes that may become completely irreversible within as small a period as 1 month. This phenomenon explains the natural progression of AF from *paroxysmal* episodes

(spontaneously resolve within 7 days) to *persistent* AF (requires medical intervention to restore NSR) and eventually to *permanent* dysrhythmia. A rhythm control strategy that aborts the progression of AF while still in the paroxysmal state may therefore obviate the need for long term intervention.

Multiple theories have been proposed to explain the development of AF and the true pathophysiology is likely multifactorial. That said, for the purposes of this article we will focus on the micro-reenty circuit model as this theory lends itself best to understanding the pharmacologic treatment of AF. In this model, AF is believed to originate via the formation of multiple micro-reentry circuits within the atria and distal-most segments of the pulmonary veins that discharge electrical signals in a very rapid and disorganized manner. The asynchronous firing of these impulses from multiple separate locations induces atrial tissue fibrillation with the consequent ventricular rate dictated by the variability of their transmission through the AV node. While the exact pathophysiology is not completely understood, we do know that these re-entry circuits depend upon fast-type sodium channel conduction to persist and occur far more commonly in both diseased and/or stressed tissues and those that exhibit shorter durations of electrical refraction.[2] It is due to these phenomena that both class I and III agents can be used to successfully terminate AF.[9] The recent discovery of various ion channels that exist only within atrial and not ventricular tissues has allowed the development of atrial selective agents that can safely and effectively convert AF without the potentially catastrophic ventricular side effects of their older counterparts.

The first approach to show real promise is blockade of the atrial specific sodium channel. Ranolazine, initially developed and approved by the FDA as an anti-anginal medication in 2006, has been the most studied agent. While several animal-based studies have demonstrated successful termination of AF, adequate human studies are lacking and ranolazine currently does not have FDA approved for use as an anti-dysrhythmic in the US.[10, 11] That said, there are a few clinical studies worth mentioning. The MERLIN trial investigated the role of ranolazine as an anti-anginal agent in over 6500 patients with moderate to high risk ACS. While there was no significant benefit demonstrated for patients with ACS, it was serendipitously discovered that the long-term daily use of ranolazine led to a significant reduction in ventricular dysrhythmias (absolute risk reduction of 3.0% [$p<0.001$]) and a trend towards a significant reduction in the development of new onset AF (absolute risk reduction of 0.7% [$p=0.08$]).[12, 13] Another interesting study out of India looked at 18 patients who presented with new or paroxysmal AF of less than 48h duration. Each patient was given a single dose of 2000 mg of PO ranolazine and observed for a period of 6 hours. Thirteen patients converted to NSR within this time period and there were no reports of either ventricular dysrhythmia or hemodynamic compromise.[14] While neither of these studies supports the use of ranolazine for the safe and rapid conversion of AF within the emergency department, they do suggest a definite need for further research into the role of atrial-selective Na^+ channel blockade.

Atrial-selective blockade of the inward rectifying potassium channel provides an alternative target for the pharmacologic cardioversion of patients with AF. Vernakalant, a novel atrial-selective class III agent with some additional rate-dependent and atrial-selective class I effects, has been the most studied medication. The ACT trials (I-IV) were designed to evaluate the efficacy of IV vernakalant in terminating recent onset AF. The ACT I trial randomized over 200 patients with new onset AF of < 45 days duration to attempted cardioversion with IV vernakalant. Focusing upon the subset of patients who presented with AF of less than 48 hour duration, 62% ($p<0.0001$) converted to NSR within 90 minutes of treatment with a median conversion time of only 11 minutes. Furthermore, 93% of the converted patients remained in NSR for a duration of at least 7 days.[15] The ACT II-IV trials demonstrated similar results, with successful AF conversion rates of ~50% across the board for all patients treated with IV

vernakalant. Equally encouraging, significant ventricular dysrhythmias and/or systemic hypotension occurred in fewer than 2% of all treated patients.[16]

Building upon this, the AVRO study compared IV vernakalant to a standard amiodarone infusion for the conversion of patients with recent onset AF (<48 hours). At 90 minutes after the initiation of treatment, 51.7% of the patients in the vernakalant cohort converted to NSR vs. 5.2% of patients randomized to amiodarone ($p<0.0001$). Furthermore, vernakalant remained significantly more effective than amiodarone even after extending the observation period to 240 minutes.[17] In light of these studies, vernakalant has been proven not only effective for the rapid ED conversion of patients with paroxysmal AF but in fact more effective than the currently accepted (although not FDA approved) treatment with IV amiodarone. Consequently, IV vernakalant underwent approval for use in the European Union under the trade name Brinavess™ in 2010. Prior to domestic approval, however, the FDA requested a larger phase III trial to definitively prove the efficacy and safety of intravenous vernakalant. To this end, the ACT V trial was initiated in 2009 but prematurely terminated within the following year when one of the study participants developed life-threatening cardiogenic shock following the initiation of treatment with IV vernakalant. As such, the data requested by the FDA has yet to be completed, and although initially very promising, vernakalant remains currently unavailable for use within the US.

Despite this setback, promising international research continues to emerge. A group from Argentina has recently published several studies comparing vernakalant to the more conventional anti-dysrhythmics. In these studies, IV vernakalant converted patients with recent onset AF (<48 hours) to NSR significantly faster than either IV flecainide or IV propafenone resulting in shorter total hospital stays with no reported major adverse cardiovascular events.[18,19,20] Another group from Germany compared IV vernakalant to IV amiodarone as a pharmacological adjunct for the electrical cardioversion (ECV) of patients with persistent AF. Although early, the results of this small study suggest that vernakalant is significantly more effective than amiodarone for the maintenance of NSR following ECV (73% vs. 33%, $p=0.028$).[21] Given this growing body of success, the future of atrial-selective class III agents remains very intriguing and their future use in domestic EDs is all but certain as further clinical investigations push forward.

The final of the novel anti-dysrhythmics is the class III agent dronedarone. Initially approved by the FDA in 2009 for the treatment of patients with AF/A-Flutter, dronedarone was designed as a safer alternative to long-term amiodarone use. The addition of a sulfonyl side chain to its molecular structure drastically reduces its circulating half-life to under 24h (compared to several weeks with amiodarone) thereby significantly limiting the potential for neurologic toxicity. In addition, removal of the iodine content eliminates the potential for significant thyroid toxicity. Finally and noteworthy, although currently the most commonly used agent for long-term rhythm control in patients with chronic AF, amiodarone has never received FDA approval for this purpose.

Studies investigating dronedarone in the long-term management of patients with paroxysmal AF have been less than encouraging. The ANDROMEDA trial, designed to investigate the use of dronedarone in patients with CHF, was terminated early due a significant increase in all-cause mortality in the treatment cohort. [26] In a similar manner the PALLAS trial, designed to examine the clinical outcomes of patients with permanent AF treated with chronic dronedarone therapy, was also terminated early secondary to significant elevations in the reported incidence of stroke, cardiovascular mortality, and hospitalization rates in the treatment arm. These trials have raised serious questions regarding the appropriate long-term use of dronedarone in various patient cohorts. In light of this, and until an IV formulation is approved for the rapid conversion of patients with AF in the ED, dronedarone

will remain more of a curiosity on medication reconciliation forms and less of a practical option for emergency physicians. That said, further research into the role of this agent and the subsequent development of similar medications in this class will likely have an impact on the clinical practice of emergency medicine in the not too distant future.

ACUTE CORONARY SYNDROME AND THE NEW ANTICOAGULANTS

Acute coronary syndrome (ACS) accounts for over 1.1 million hospitalizations and 400,000 fatalities per year in the US and CAD-related complications remain the leading cause of death in this country. Not surprisingly, an extensive sum of scientific inquiry and monetary investment is continuously dedicated to the further development of medications designed to improve the clinical outcomes of these patients. As the formation of an intraluminal coronary artery thrombosis with secondary distal ischemia is the inciting event in ACS, the primary focus in the emergent management of these patients has been upon finding agents that will more rapidly reduce the overall clot burden and thereby restore downstream myocardial perfusion. Not surprisingly, as the potency of these drugs continues to increase, so does the incidence of secondary bleeding complications. Initially considered an acceptable casualty of myocardial tissue salvage, accumulating evidence has illuminated the true clinical significance of these bleeding events.

After dissecting the numbers, roughly 30% of all patients with ACS will experience a major bleeding episode. Of note, these events have been shown to independently increase mortality rates by approximately 6-fold. [28] In light of this, multiple studies have attempted to identify which patients are most likely to bleed in order to develop guidelines for modified treatment approaches. The majority of these studies agree upon the following non-modifiable risk factors: female sex, age > 70, baseline renal insufficiency, elevated cardiac markers, and ST segment changes > 1mm from the baseline.[29] It is our duty as practicing emergency physicians to identify these high risk patients and use medications that can safely open their occluded coronaries without increasing their risk for significant hemorrhage. As expected, this need for safer alternatives has not gone unnoticed by the pharmaceutical industry, and multiple classes of novel medications have been investigated to fill this role.

Anticoagulants have remained a cornerstone in the management of ACS since the late 1940's when pioneering studies cemented the role for unfractionated heparin (UFH) in patients with myocardial infarctions.[30] The low molecular weight heparins (LMWH) gained wide-spread clinical acceptance in the mid-1990's and were rapidly introduced into ACS treatment algorithms. The major benefit of the LMWHs is their improved dose-to-response predictability as compared to UFH. This feature is intrinsic to the composition of LMWH in that a given sample contains a significantly higher percentage of polysaccharide chains featuring the specific pentasaccharide sequence necessary for antithrombin III (AT3) activation versus a random sample of UFH. Building upon this, the novel agent fondaparinux was developed as a synthetic form of the target pentasaccharide sequence in order to create an even more predictable anticoagulant. Approved by the FDA in 2001, the role of fondaparinux in the treatment of ACS has undergone extensive research over the past 10 years with compelling results with the two studies of greatest importance outlined below.[31]

The OASIS 5 trial randomized over 20,000 patients with either unstable angina (UA) or non-ST elevation MI (NSTEMI) to anticoagulation with either fondaparinux or standard LMWH. Although the results demonstrated statistical equivalence between the two medications with regards to ischemic complications, there were significant reductions in both the incidence of major bleeding complications

at the 9-day mark (2.2% vs. 4.1%, p<0.001) and 30-day mortality rates (ARR 0.6%, p=0.02) in the fondaparinux cohort.[32] In light of this, the OASIS 6 trial was designed to explore the role of fondaparinux in the treatment of patients with ST elevation MI (STEMI). Over 12K patients were randomized to anticoagulation with either fondaparinux or a standard UFH infusion. While there was a non-significant trend towards fewer major bleeding complications in the fondaparinux cohort (1.8 vs. 2.1%, p=0.14), this was overshadowed by prominent but not statistically significant increases in both re-infarction and mortality rates at the 30-day point in fondaparinux patients who subsequently underwent PCI. This finding was most likely secondary to significant escalations in the rates of both guiding catheter thromboses (22 vs. 0, p<0.001) and comprehensive coronary complications (270 vs. 225, p=0.04) in the fondaparinux cohort.[33] Taken as a whole, these results suggest that fondaparinux is equally as effective as - and safer than - standard treatment with LMWH in patients with UA/NSTEMI but that its use should be avoided in patients with STEMI undergoing PCI given the increased risk for post-procedural thrombotic complications. As many patients with NSTEMI may undergo PCI at some point during their hospitalization, a careful discussion with the consulting cardiologist is necessary to determine the likely timing of said intervention, as patients undergoing PCI within the first 24 hours of presentation may benefit from initial treatment with UFH rather than fondaparinux.

An alternative class of anticoagulants, the direct thrombin inhibitors (DTI), began to see serious clinical use in the late 1990's. The DTI's are attractive in theory as they function independent of circulating AT3 and therefore should exhibit a significantly more predictable dose-response curve. Soon following their introduction, clinical trials were undertaken to determine the role of these agents in the management of ACS. Bivalirudin, approved by the FDA for clinical use in 2000, has been the most extensively researched of this class.[34]

Relevant to the practice of emergency medicine, the ACUITY trial examined nearly 14,000 patients with NSTEMI undergoing early PCI and randomized them to anticoagulation with either UFH/LMWH + GPI, bivalirudin + GPI, or bivalirudin monotherapy. Although the rates of ischemic complications were statistically equivalent across all 3 cohorts (7.3% vs. 7.7% vs.7.8% respectively), there was a significant reduction in the incidence of major bleeding complications in patients treated solely with bivalirudin (5.7% vs. 5.3% vs. 3.0%, p<0.01).[29] Finally, the HORIZONS-AMI trial randomized over 3600 patients with STEMI undergoing emergent PCI to anticoagulation with either UFH/LWMH + GPI or bivalirudin monotherapy. Of interest, there was a significant reduction at the 30-day mark in both ischemic complications (9.2% vs. 12.1%, p=0.005) and major bleeding events (4.9% vs. 8.3%, p<0.001) in the bivalirudin cohort in addition to a significant reduction in all cause mortality (2.1% vs. 3.1%, p=0.047).[36] That said, there was also a significant increase in the rate of acute stent thrombosis in the bivalirudin arm at the 24 hour mark (21 vs. 4, p<0.001). Consequently, although bivalirudin appears promising for patients with ACS undergoing urgent or emergent PCI, more research is necessary to determine if the use of an adjunctive anticoagulant is required within the first 24 hours of revascularization.

A final novel class of anticoagulants worth mentioning is the direct Factor Xa inhibitors (FXI). While the majority of interest in this class has focused upon oral medications designed for long-term outpatient therapy (i.e. rivaroxaban/Xarelto® and apixaban/Eliquis®), otamixiban was a parenteral agent in phase III development for use in patients with ACS. Theoretical benefits included a rapid onset, predictable pharmacokinetics, and a short circulating half-life.[31] That said, the TAO trial investigating over 13K patients with NSTEMI failed to show a significant reduction in ischemic complications compared to standard therapy with UFH + GPI at the expense of a significant increase in major bleeding episodes, and consequently the further development of this drug has been halted by the manufacturer as of June 2013.[37]

In summation, over 50 years of experience and experimentation into finding more aggressive and effective ways to open occluded coronaries has inevitably led to an increased prevalence of secondary bleeding complications. Once assumed an acceptable complication, more recent studies have uncovered the true clinical significance of these events prompting an aggressive search to identify novel classes of anticoagulants that may limit future bleeding episodes. As is true with the majority of pharmacological studies, not every agent will pan out, as noted with the Factor Xa inhibitors above. That said, fondaparinux has shown promise for anticoagulation in patients with UA/NSTEMI who are not undergoing PCI, whereas bivalirudin may become the anticoagulant of choice in patients with STEMI undergoing PCI.

Obstruction of the coagulation cascade has not been the only pathway investigated in the treatment of ACS. Agents that inhibit the function of platelets have been used to reduce myocardial ischemia since the early 1950's when regular aspirin use had been shown to be effective for decreasing the incidence of MI.[38] Aspirin is so effective in this role that it still remains a mainstay in the current management of ACS . That said, alternative targets for platelet inhibition have been identified in the 60-year interim and newer classes of medications have been developed to take advantage of this. The most extensively studied of these agents, thienopyridines, impair platelet activity via blockade of the ADP receptor, a pathway distinct from that targeted by aspirin, and nowadays both types of agents are typically used synergistically in patients with ACS.

Clopidogrel, a second generation thienopyridine approved by the FDA in 1997, is the prototypical agent in this class. Of note, clopidogrel is functionally a prodrug that requires in-vivo conversion to its active form by the CYP-450 system. Once active, it irreversibly inhibits platelet activity with a circulating half-life of ~8h. Published in 2005, the CLARITY trial examined the role of clopidogrel in addition to standard therapy with aspirin and fibrinolytics in patients with STEMI.[39] A subset analysis of study patients who additionally underwent PCI, the CLARITY-PCI trial, demonstrated significant reductions in both ischemic complications and mortality rates in those patients randomized to treatment with clopidogrel prior to PCI (3.6% vs. 6.2%, p=0.008) without a corresponding increase in major bleeding events (2.0% vs. 1.9%, p>0.99).[40]

Given that clopidogrel requires in-vivo activation, there has been a lot of debate regarding the necessity of a loading dose in patients with ACS. A subanalysis of the HORIZONS-AMI data looking at patients with STEMI undergoing PCI found significant reductions in re-infarction (1.4% vs. 2.6%, p=0.01) and mortality rates (2.0% vs. 3.2%, p=0.03) at the 30-day mark in those patients given a 600 mg load as opposed to 300 mg without any corresponding increase in significant hemorrhagic complications.[41] A subsequent study investigating the ideal loading dose found no significant difference in the degree of platelet inhibition between patients loaded with 600 mg vs. 900 mg.[42] As such, a 300 mg loading dose is most commonly used in patients with ACS who are not undergoing PCI whereas a 600 mg load is reserved for those who are. It is prudent to avoid a loading dose in patients over the age of 75 due to a presumed increase in the likelihood of bleeding complications, opting rather to initiate therapy with a standard 75 mg dose.

The second major concern regarding clopidogrel use relates to data from the CURE Trial that suggests that patients given this drug within 5 days of undergoing CABG suffer from a significant increase in major hemorrhagic events.[43] Although the bulk of subsequent literature has proven less conclusive, the current AHA STEMI guidelines cite the need to withhold treatment with clopidogrel for 5 days prior to CABG as a class I recommendation.[44] Short of performing bedside angiography though, it is impossible

in the emergency department to predict which patients with ACS will require subsequent coronary bypass. Furthermore, as discussed earlier, sound clinical data has proven the benefit of administering a clopidogrel load to patients prior to undergoing PCI. Fortunately, a recent 2011 meta-analysis of 34 studies involving over 22K patients found no significant increase in death, MI, or CVA in patients given clopidogrel within 5 days prior to CABG (OR 1.10, 0.87-1.41 95% CI).[45]

Newer anti-platelet agents have been developed to address some of the perceived shortcomings of clopidogrel. Prasugrel, a third generation thienopyridine approved by the FDA in 2009 as an antiplatelet adjunct for PCI, has received the most attention. Its function is analogous to clopidogrel as it irreversibly inhibits platelet activation, but undergoes much quicker in-vivo conversion to its active metabolites thereby theoretically inducing a more rapid inhibition of platelet function and a secondary reduction in ischemic complications.[46] While attractive in theory, the available clinical data has not been supportive. The JUMBO trial looked at over 900 patients undergoing elective or urgent PCI randomized to clopidogrel vs. prasugrel and demonstrated a non-significant reduction in adverse cardiac events (7.2% vs. 9.4%, p=0.26) at the expense of a similar non-significant increase in major bleeding complications (1.7% vs. 1.2%, p=0.59) in the prasugrel group. [47] Similar results were obtained in the TRITON trial which randomized over 13K patients with ACS scheduled for PCI to treatment with either clopidogrel (300mg LD/75mg after) or prasugrel (60mg LD/10mg after). The cohort randomized to prasugrel demonstrated a significant reduction in major adverse cardiac events (9.9% vs. 12.1%, p<0.001) at the expense of a significant increase in major bleeding complications (2.4% vs. 1.8%, p=0.03). In addition, the incidence of bleeding-related fatalities was dramatically increased in the prasugrel cohort (21 vs. 5, p=0.002), and an examination of all cause mortality failed to show any significant difference between the two treatment arms (3.0% vs.3.2%, p=0.64).[48]

Where prasugrel has been essentially a disappointment, ticagrelor, an even newer anti-thrombotic agent approved by the FDA in 2011 for the treatment of patients with ACS, has shown significant promise. Unlike the thienopyridines, ticagrelor does not require in-vivo conversion to an active metabolite and therefore in theory should induce a more rapid inhibition of platelet function. Even more importantly, ticagrelor binds to the ADP receptor in a reversible manner with a circulating half-life of only 7 hours. This makes it an extremely attractive initial option in patients who may require subsequent invasive procedures including CABG. Clinical studies designed to show this benefit have unfortunately yet to be completed. One study of note, the PLATO trial, randomized over 18K patients admitted with ACS to long-term treatment with either clopidogrel or ticagrelor. At the 12-month mark, patients randomized to ticagrelor exhibited a significant reduction in major cardiac events (9.8% vs. 11.7%, p<0.001) without a corresponding significant increase in major bleeding events (11.6% vs. 11.2%, p=0.43).[49] Subsequent sub-analyses showed that this difference was not related to individuals who were poor metabolizers of clopidogrel and likely represented a true benefit for treatment with ticagrelor. [50] Although very encouraging, this study followed patients over a 1-year period thereby limiting the interpretation of its benefit for the ED patient population and further studies remain necessary to better identify the specific role for ticagrelor within emergency medicine.

THE NEW ANTI-HYPERTENSIVES

Although hypertension is an exceptionally common condition affecting nearly one-third of the adult US population, fewer than 1% of hypertensive patients will ever experience a true hypertensive emergency.[51] Rare as it may be, patients with hypertensive emergency require immediate intervention

to carefully yet aggressively reduce their mean arterial pressure and limit further tissue injury. While there are numerous agents commonly available for rapid BP reduction within the emergency department, the prudent physician will always attempt to tailor the treatment to the individual patient and specific organ system(s) involved.

Clevidipine is a recently developed 3rd generation IV dihydropyridine approved by the FDA in 2008 for use as an antihypertensive agent. Analogous to older dihydropyridines, clevidipine selectively dilates the peripheral arterial circulation thereby decreasing the cardiac afterload without significant effects on either myocardial contractility or preload. Due to the incorporation of an ester linkage in its molecular structure, clevidipine is rapidly metabolized by circulating plasma esterases with an effective half-life of less than one minute. This characteristic lends to two obvious benefits, namely that the antihypertensive effects of clevidipine can be rapidly reversed via simply stopping the infusion, and that the appropriate dosing of this agent does not require adjustment in patients with underlying hepatic or renal pathology. Of note, clevidipine is only available compounded with a lipid emulsion and may require occasional IV line changes for prolonged infusions.[52]

Although relatively new, several clinical trials have explored the utility of this agent in patients with severe hypertension. The ESCAPE-1 and 2 trials looked at over 350 patients with peri-operative hypertension and compared the efficacy of clevidipine to placebo for blood pressure regulation. In both studies, over 90% of the clevidipine subjects achieved adequate blood pressure control while fewer than 25% did so with placebo.[53, 54] Focusing upon the emergency medicine literature, the VELOCITY trial was a single arm study that looked at the use of clevidipine in 126 ED and ICU patients with severe hypertension. In this study, 88.9% of subjects met their blood pressure goals within 30 minutes of treatment initiation with a median time of 10.9 minutes. Furthermore, 92.3% of patients met their target BP goal with clevidipine as the sole antihypertensive agent, and 91.3% of patients were successfully transitioned to oral antihypertensive medications without further complication.[55]

The ECLIPSE trial revisited the use of clevidipine in peri-operative hypertension, this time comparing clevidipine head-to-head with nitroprusside, nitroglycerine, and nicardipine infusions. Clevidipine was able to maintain significantly tighter blood pressure control as compared to nitroprusside and nitroglycerine and was equally as efficacious as nicardipine. Adverse events reported in the clevidipine cohort were equal to those treated with nicardipine and nitroglycerine and significantly less than those treated with nitroprusside.[56] Finally, a recent study looking at the use of prolonged clevidipine infusions demonstrated no significant increase in severe adverse effects from a 72 hour infusion in patients with mild-moderate hypertension when compared to placebo. Furthermore, the elimination half-life of clevidipine was no different in patients following the 72 hour infusions as compared to patients given a 20-minute infusion, and there were no reports of significant rebound hypertension within a 6 hour observation period following the cessation of therapy. Occasional hypertriglyceridemia was noted with infusions beyond 72 hours but resolved within 8 hours of stopping treatment in all cases and there were no documented adverse complications.[57]

Although in its clinical infancy, early studies with clevidipine have shown it to be an extremely safe, efficacious, and efficient method to reduce blood pressure in hypertensive emergencies and its presence in the management of said patients in the emergency department is all but certain to expand. Promising ongoing studies are attempting to determine the role of clevidipine in ED patients with hypertensive associated subarachnoid hemorrhage and hypertensive associated acute heart failure.[58, 59]

CONCLUSIONS

As cardiovascular emergencies account for the leading cause of morbidity and mortality in this country, further research into agents that may improve patient outcomes will continue at an exceptionally aggressive pace. Newer agents will continue to flood the market often leaving the practicing emergency physician with more questions than answers. The old aphorism that you never want to be the first one or the last one to a party certainly holds true, and the astute clinician will need to maintain a certain familiarity with these agents and their proper use within the emergency department in order to ever improve our patients' wellbeing. The identification of atrial specific ion channels and subsequent development of drugs designed to target them will most certainly impact the emergent management of AF in the not too distant future. Fondaparinux and bivalirudin will likely become more prevalent as the anticoagulants of choice in patients with ACS as the true clinical significant of the bleeding complications commonly seen with UFH and the LMWHs continues to be uncovered. Ticagrelor has shown promise as the antiplatelet agent of the future for patients in the ED with ACS given its rapid onset and reversible nature. Finally, clevidipine will most assuredly have an evolving role in the management of hypertensive emergencies given its rapid onset, easy titratability, and lack of significant side effects.

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