Clinical Experience With Intravenous Angiotensin II Administration:

A Systematic Review of Safety

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SUPPLEMENTAL DIGITAL CONTENT 4

Effects of Angiotensin II by Organ System

Cardiovascular

The majority of cardiovascular studies reported that angiotensin II (ATII) infusion increased blood pressure. In some studies, blood pressure was not reported or ATII was intentionally administered at a subpressor dose. Doses eliciting blood pressure increases of at least 5% ranged from 0.5 to 75 ng/kg/min. The maximum average increase in mean arterial pressure (MAP) reported in normotensive healthy volunteers was 36% among 8 volunteers after they received a fixed dose of 10 ng/kg/min for 15 minutes (1). Another study reported a mean 50% increase in systolic blood pressure (SBP) in a group of 6 healthy volunteers during infusions of ATII at 1 to 3 µg/min (2). Among 28 patients with hypotension resulting from various etiologies, ATII administered at 0.3-60 µg/min (mean 14.1 µg/min) induced an average increase in MAP of 48% (3). ATII was also reported to increase MAP by 70% and SBP by 69% in 6 patients with hypotensive shock (4), although the ATII dose and duration of administration were not provided.

None of the studies specifically designed to evaluate pressor response was associated with ATII-related serious adverse events (SAEs). Most studies examining physiological effects of ATII other than increased blood pressure reported an increase in blood pressure, often using a dose adjustment protocol until a predetermined pressor response was achieved, eg, an increase in MAP of 10-20 mm Hg. In total, 36 studies investigated ATII effects on hypotension resulting

from a medical condition, including 13 reports that documented the therapeutic use of ATII in the management of hypotension associated with shock (3−15).

Increased blood pressure was not confined to the systemic circulation. Small increases in pulmonary vascular resistance in response to ATII have been reported together with increased ventricular pressure (16) and changes in pulmonary artery ejection parameters (17) in healthy volunteers. These changes are consistent with a pressor response in the pulmonary vascular bed without effects on aorta ejection parameters (16−18). Johnson et al analyzed ATII's effect on cutaneous circulation and found that skin temperature of the forehead, forearm, abdomen, and ankle dropped within 3 minutes as blood pressure rose. Interestingly, oxygen consumption did not increase, but a compensatory increase in arteriovenous oxygen consumption was noted (19). Jorneskog et al found that ATII infusion increased heat-induced microvascular hyperemia in the skin of normal subjects but that patients with familial hyperlipidemia were resistant to this effect (20). In addition, healthy volunteers with a G protein 3 subunit 825T allele polymorphism, which is significantly associated with an increased risk for hypertension, showed enhanced vasoconstriction in the skin microcirculation in response to ATII (21). ATII infusion as an angiotensin sensitivity test during pregnancy also increases uterine vascular resistance (22−24) but has been shown to be safe in patients with normal ATII responsiveness (23, 24). Doppler ultrasound has demonstrated a transient ATII-induced increase in cerebral artery flow velocity in healthy subjects (25) and normotensive primiparous women (26). However, the change in flow velocity was thought to be related to the rise in blood pressure following ATII infusion rather than a direct effect of ATII on the cerebral circulation.

Myocardial function and systemic hemodynamics were evaluated in a number of studies. In 2 studies, Magrini et al (27, 28) evaluated the effects of ATII on coronary hemodynamics in patients with mild essential hypertension. Coronary sinus blood flow increased at 13 ng/kg/min ATII but decreased at a dose of 3 ng/kg/min. Additionally, myocardial oxygen supply decreased at rest and during exercise at an ATII dose of 3 ng/kg/min, but it increased under both conditions with a dose of 13 ng/kg/min. In contrast, another study found that coronary blood flow, myocardial arteriovenous oxygen difference, and myocardial oxygen consumption changed very little after ATII infusion, while arterial pressure increased 25% (19). Nolan et al demonstrated decreased cardiac output at an ATII dose of 33 ng/kg/min, with concomitant dose-dependent decreases in splanchnic and renal blood flow (29). One study documented an increase in

afterload in patients with angina pectoris who were administered 0.075 ng/kg/min ATII (30), while another found increased central pulse pressure and reduced cardiac index after administration of varying doses of ATII (1).

In 1941, Bradley et al administered ATII ("angiotonin" purified from a natural source) and observed a decrease in cardiac output as a result of bradycardia, as well as increased peripheral resistance and mean arterial pressure via arterial vasoconstriction (31). This study also observed a decrease in arterial elasticity with the smallest dose and a dose-dependent increase in elasticity with higher doses. Johnson et al found that the normal vasodilatory response of skeletal muscle to exercise was unchanged with ATII administration and postulated that during exercise, vasoconstriction is largely restricted to visceral organs and nonexercising muscles (19). In this study, 1 subject experienced orthostatic hypotension after an ATII infusion was stopped; arterial pressure was restored with reinfusion of ATII. Other studies have evaluated myocardial contractility with mixed results (1–4, 7, 19, 30, 32–41). Ambiguity in this respect is likely related to a multitude of ATII receptor phenotypes (42). Other studies examined peripheral vascular changes with local ATII administration (43, 44) and demonstrated the presence of peripheral ACE activity (45). Baroreflex response to ATII has been evaluated in multiple settings (46-56), including 2 groups that used ATII administration to study arousal and baroreflex sensitivity during sleep (46, 47). In a more recent study involving 12 healthy subjects, ATII infusion over 6 hours (mean infusion rate, 10.9 ± 1.3 μg/hour) increased steady-state plasma ATII concentrations and sustainably reset the baroreflex set point toward persistently higher blood pressure levels over a period of 1 to 2 hours after cessation (56). ATII has been studied extensively in combination with ACE inhibitors, angiotensin II receptor inhibitors, and other modulators of the RAAS to compare activities of these agents and to elucidate homeostatic mechanisms (57-62).

Endocrine

ATII has been associated with endocrine effects in multiple studies. Reviews by Romero et al (63, 64) summarized evidence that ATII stimulates oxidative stress via endothelin production and formation of F2-isoprostanes, which ultimately potentiates its hypertensive effect. Plasma atrial natriuretic peptide (ANP) was found to be increased with ATII administration in several studies (35, 41, 65–68) but not in another (69). Production of these

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substances is closely related to ATII's physiologic role as a vasopressor; each associated study reported no SAEs.

ATII is a cornerstone of the RAAS and stimulates secretion of aldosterone. Increased plasma aldosterone was reported in 182 studies using ATII doses from 0.5 to 20 ng/kg/min (see table in **Supplemental Content 2**). None of the studies reported SAEs. In 6 patients with primary hyperaldosteronism due to aldosterone-producing adenomas, ATII infusion did not further stimulate aldosterone secretion (70). Following chronic treatment with dexamethasone in 2 patients with primary hyperaldosteronism, aldosterone secretion was responsive to exogenous ATII (71).

Another physiologic effect commonly noted was decreased renin as a result of the sustained negative feedback by continuous infusion of ATII. This effect was noted in 10 studies (62, 72−80), none of which reported any SAE associated with low renin activity or ATII administration. One study evaluated angiotensin infusion as a means to control blood pressure in participants with normal- or high-renin essential hypertension (80).

Several studies demonstrated increased plasma arginine vasopressin after ATII infusion (66, 81−84). Matsukawa et al noted an increase in vasopressin that was blunted with concomitant infusion of nitroprusside and atrial natriuretic peptide (82). Phillips et al also noted increased vasopressin associated with thirst after ATII administration (83). Oxytocin levels were increased in 2 studies, with exogenous ATII rising to 36% and 41% above baseline in 27 and 7 healthy men, respectively (81, 85). Other pituitary hormones were increased in response to ATII, including growth hormone, adrenocorticotropic hormone (ACTH), and luteinizing hormone, the latter spiking when ATII was administered in the mid-luteal phase (86, 87). Chiodera et al cited other studies showing angiotensin-like immunoreactivity in clusters of nerves and fibers in the posterior pituitary and in vitro stimulation of neurohormone release from posterior pituitary cells by ATII (81). Two studies documented decreases in ACTH with ATII infusion (88, 89). Grant et al found that decreases in plasma ACTH and cortisol after ATII infusion were accompanied by an increase in intact parathyroid hormone. The authors speculated that ATII exerted an indirect effect on the parathyroid gland that was mediated by changes in serum ionized calcium (88).

Mediskou et al evaluated the relationship between nontumoral hyperprolactinemia and RAAS activity (90). Increased levels of aldosterone and prolactin and decreased levels of cortisol

occurred with ATII infusion but were reversed after administration of a dopamine agonist. No SAEs were reported. Arafah et al reported that 6 subjects with prolactin-secreting pituitary tumors were more sensitive to ATII pressor effects than 5 normal subjects in both high- and low-sodium states (91). A heightened adrenal response (increased plasma aldosterone) to ATII was observed only after a sodium load.

Serum erythropoietin concentration also increased after ATII infusion, presumably from increased synthesis in the kidney (92, 93). The dose-dependent increase in erythropoietin was mitigated with concomitant administration of losartan, but not with captopril. Other investigators demonstrated an increased renal synthesis of prostaglandins PGE_2 and 6-keto-$PGF_{1\alpha}$ (84), as well as the stimulation of PGE_2 excretion in urine (94) following ATII administration. Conversely, administration of PGE1 or PGE2 at the same time as ATII blunted ATII pressor effects in pregnant subjects (95–97).

In a study of patients with essential hypertension, free fatty acids (FFA) increased in overweight patients but not normal-weight patients (98). The increase in FFA showed no relation to the dose of ATII. Lastly, ATII increased glucose utilization and clearance and insulin secretion (99). This mechanism, detailed by Buchanan et al, involved ATII-induced redistribution of blood flow away from insulin-independent tissues (kidney), and toward insulin-dependent tissues (skeletal muscle).

Pulmonary

A few studies assessed the effect of ATII on the pulmonary vasculature. Circulating ATII is supplied primarily by conversion of angiotensin I to angiotensin II in the pulmonary vasculature by ACE and by an ACE-inhibitor–resistant chymase-like activity (100). Studies in healthy volunteers demonstrated that pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure (MPAP) increase in tandem with systemic vascular resistance and blood pressure (17, 18, 35, 41). Similar increases in MPAP and PVR were induced by 30 minutes of hypoxia (75%-80% arterial oxygen saturation) or a pressor dose of ATII (6 ng/kg/min) for 30 minutes. When ATII was introduced under hypoxic conditions, the change in MPAP was less than additive, and there was no further increase in PVR over ATII alone (35). Similarly, reductions in minute ventilation induced by exogenous ATII and by hypoxia, hypercapnia, or a cold pressor stimulus were less than additive when combined in healthy subjects (101-103).

Thus, in contrast to results in animal models, acute pressor doses of ATII in humans do not seem to potentiate pulmonary vasoconstrictor and ventilator responses to chemoreflex stimuli.

Angiotensin II exacerbated asthma via bronchoconstriction in 2 studies (102, 103). Millar et al demonstrated bronchoconstriction after ATII infusion at 4 and 8 ng/kg/min in 8 patients with mild asthma, 5 of whom reported side effects of cough and chest tightness (102). Additionally, endogenous levels of ATII were elevated in 9 subjects with acute severe asthma. In another study by the same group, ATII significantly potentiated methacholine-induced bronchoconstriction in mild asthmatics at a subthreshold dose of 2 ng/kg/min (103). Both studies noted that the exact mechanism by which ATII causes bronchoconstriction is unknown, but they cited other investigations that proposed a role of inflammatory mediators like histamine and prostaglandin. Wheezing was reported in 1 of 10 patients with distributive shock receiving ATII in addition to norepinephrine for hemodynamic support (104).

Renal

ATII has been associated with decreased glomerular filtration rate (GFR), decreased renal plasma flow, and antinatriuresis. Decreased GFR following ATII administration was cited in 11 studies via an effect on the filtration barrier (79, 84, 105−113), although 2 studies did report a significant increase in GFR following ATII infusion at 0.5 and 3.0 ng/kg/min in normotensive and hypertensive volunteers (114, 115). An ATII dose of 8 ng/kg/min was reported to induce alterations in glomerular pore size, resulting in reduced excretion of several substances, including uric acid, xanthine, and oxypurinol, after an ATII (116). Another study noted increased excretion of the neurotransmitter serotonin (111). Several studies reported decreased fractional excretion of sodium (29, 62, 67, 84, 105, 109, 118−124) and increased serum potassium (125, 126). Importantly, ATII can stimulate natriuresis and diuresis in patients with cirrhosis and ascites, an effect opposite to that observed in subjects with normal liver function (127, 128). Decreased renal plasma flow, a consequence of increased vascular resistance, was cited in 17 studies (29, 33, 57, 105−109, 120–122, 129–134). Donker et al found little change in urethral pressure with a pressor dose of ATII, in contrast to changes with α-adrenergic effectors (135). When ATII was administered at 9 μg/min to a male patient with septic shock, ATII increased arterial pressure and renal vascular resistance without altering renal blood flow (15).

One death of a normal volunteer on day 6 of a continuous infusion of ATII is discussed elsewhere; this subject had sodium excretion extremes of 2 mEq/day on day 2 and 127 mEq/day on day 6 (127). Despite the changes in renal function markers with ATII administration, no organ damage or other SAEs were documented in other renal function studies.

Pregnancy

A progressive resistance to the pressor effects of angiotensin II during normal pregnancy has been documented. Schwarz et al demonstrated a decreased pressor effect and decreased heart rate reduction with incremental ATII infusion in normotensive third-trimester pregnant women versus nonpregnant women; side effects of headache, low backache, and dizziness were reported at the highest dose of 6.6 ng/kg/min (136). In a study of 192 pregnant young women (13–17 years old) and 10 normotensive nonpregnant women, Gant et al demonstrated that the dose of ATII required to induce a 20 mm Hg increase in diastolic blood pressure increased during the course of pregnancy up to 30 weeks and that the mean ATII pressor dose was greater compared with that of nonpregnant control subjects at all time points (137). However, in the subset of 72 pregnant women who developed pregnancy-induced hypertension, an increased sensitivity to ATII developed in the second half of pregnancy and prior to the onset of overt hypertension. A second study by this group demonstrated that an increase in vascular resistance to ATII in late-term normotensive pregnant women did not depend on volume expansion or a change in renin plasma levels (138).

In a study of normotensive pregnant women (24-38 weeks' gestation) with placental vascular disease identified by Doppler, Cook et al found a correlation between a positive ATII pressor response (> 20 mm Hg increase in DBP with < 20 ng/kg/min ATII) and early labor, fetal distress, and low birth weight (139). Conversely, in those women who were resistant to the pressor effect of ATII, a trend of decreasing systolic/diastolic ratio of the umbilical artery during the remainder of pregnancy was observed, consistent with normal placental growth, and was followed by good fetal outcomes.

Renal effects in pregnant versus nonpregnant women have been studied by Chesley et al, who demonstrated that infusion of ATII in pregnant women (26-35 weeks' gestation) is associated with a smaller drop in urine output and electrolyte excretion (Na and Cl) when compared to nonpregnant women or pregnant women near term (140). Inulin clearance

decreased by similar amounts in nonpregnant women and pregnant women near term (21%-28%) but decreased by a smaller amount in women at 26 to 35 weeks' gestation (8%-16%).

Finally, postpartum women (at least 5 months) who had had gestational hypertension were more sensitive to ATII in low sodium balance than those who had normotensive pregnancies; both pressor and aldosterone responses were enhanced (141).

Oncology

In a case series of 11 patients with inoperable solid tumors who were pretreated with an antihistamine and a glucocorticoid, ATII was infused with a chemotherapeutic agent (coadministered or given concomitantly) to increase blood pressure and enhance chemotherapy delivery to tumor cells (142). This method increased tumor blood flow selectively. One subject experienced headache. Similarly, in another case series, Onohara et al used ATII as a means to increase chemotherapy delivery in patients with hepatocellular carcinoma (143). Adverse events documented were peptic ulcers, abdominal pain, nausea, and vomiting. Fujii et al used ATII with similar intentions in pediatric patients with solid tumors (144). Noted side effects included headache, chest discomfort, nausea, vomiting, and myelosuppression in children receiving 2 to 8 chemotherapeutic agents. It is unknown whether these side effects were associated with chemotherapy vs ATII. With the exception of head and chest symptoms and a single report of nausea with vomiting, similar side effects have not been identified with ATII administration in the other studies included in this review.

Hematology and Immunology

Few studies have investigated the role of angiotensin II in coagulation pathways. Angiotensin II has been shown to increase circulating levels of plasminogen activator inhibitor-1 (PAI-1) (145). Increases in markers of platelet secretion (platelet expression of P-selectin and plasma levels of β-thromboglobulin), tissue plasminogen activator (tPA), and PAI-1 have been demonstrated with infusion of ATII at pressor doses (146, 147).

Ekholm et al noted elevations in IL-6, leukocyte count, and tissue plasminogen activator/plasminogen-activating inhibitor complexes (tPA/PAI-1) in subjects with familial combined hyperlipidemia vs normal subjects (148). IL-6 and leukocytes increased and tPA/PAI-1 decreased similarly in both groups with a 3-hour infusion of ATII at 2 ng/kg/min. However, in

this study ATII was not associated with short-term thrombin generation. Another study showed that the inflammatory mediators IL-6 and F2-isoprostanes increased with a 3-hour infusion of ATII, but that pretreatment with the mineralocorticoid antagonist spironolactone inhibited angiotensin II induction of IL-6 (149). Increases in F2-isoprostanes and blood pressure with ATII were unaffected by spironolactone.

No SAEs were reported in any of these studies.

Neurology

Investigations on the effect of ATII on the autonomic nervous system primarily demonstrated a potentiating effect. ATII has been found to have a central stimulating action on the sympathetic vasomotor system, leading to vasoconstriction of vessels in the hand (150). Likewise, Matsukawa et al concluded that ATII infusion blunted the baroreflex-mediated reduction in muscle sympathetic nerve activity (151, 152). Other studies have reported similar amplified pressor responses (153) and increased venoconstriction (154). One study in healthy volunteers demonstrated an increase in heart rate and decrease in heart-rate variability when sodium nitroprusside was added to reverse the pressor response to an ongoing ATII infusion; these results support a direct inhibition of efferent cardiac vagal activity by angiotensin II in the absence of baroreceptor activation (155). Seidelin et al found that subpressor doses of ATII did not potentiate enhancement of NE release by tyramine (156) or via physiological stimuli affecting sympathetic nerve activity (157). Simulated microgravity reduced the ATII pressor response in a study performed to elucidate mechanisms responsible for the orthostatic intolerance observed following space flight (158). None of the aforementioned studies noted any SAEs.

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