**Clinical Experience with Intravenous Angiotensin II Administration:  
A Systematic Review of Safety**

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**SUPPLEMENTAL DIGITAL CONTENT 3**

**Increases in Plasma Aldosterone Concentration**

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| **Author and Year** | **Study/Dose Typea** | **Subjects (N)** | **Dietary Sodium (mEq/day)** | **Angiotensin II Infusion Rateb** | **Aldosterone Responsec (fold change, ATII/Baseline)** |
| --- | --- | --- | --- | --- | --- |
| Conlin 1998 [32] | 1 group/incremental | Normal (17) | 10 | 3 ng/kg/min | Positive (graph) |
| degli Uberti 1990 [37] | 1 group/incremental | Normal (7) | 90 | 16 ng/kg/min | 6.1 |
| degli Uberti 1991 [38] | 1 group/incremental | Normal women (6) | 90 | 16 ng/kg/min (midfollicular phase) | 5.5 |
|  |  |  |  | 16 ng/kg/min (midluteal phase) | 4.8 |
| Eiskjaer 1992 [44] | 1 group/fixed | Healthy volunteer (11) | Ad libitum | 1.5 ng/kg/min | 3.4 |
| Fallo 1989 [49] | 2 groups/incremental | Primary hyperparathyroidism (5) before and after surgery | 120-150 | 4 ng/kg/min | Positive (graph)d |
|  |  | Age- and sex-matched controls (5) |  |  | Positive (graph) |
| Finn 1993 [52] | 1 group/incremental | Normal (28) | Ad libitum | 8 ng/kg/min | 2.7 |
| Fraser 1980 [54] | 1 group/incremental | Primary hyperaldosteronism (4) | – | 2 ng/kg/min | Mixed (graph) |
| Freudenthaler 1999 [56] | 1 group/target | Healthy (12) | – | 1-3 µg/min to PD20 (systolic) | 4.6 |
| Golub 1976 [66] | 1 group/fixed | Healthy (5) | 150 | 5 ng/kg/min | 3.5 |
| Gordon 1987 [69] | 1 group/fixed | Patients with aldosterone-producing adenoma (14) | – | 2 ng/kg/min | 6/14 responsive |
| Gordon 1994 [71] | 1 group/fixed | Modulating HTNe (90) | 10 | 3 ng/kg/min | Positive (graph) |
|  |  | Nonmodulating HTNe (60) |  |  | Positive (graph) |
| Grant 1992 [72] | 1 group/incremental | Healthy (8) | 200 | 10 ng/kg/min (high Na, Ca) | 2.4 |
| Ichikawa 1976 [76] | 2 groups/fixed | Normal (9)  Normotensive acromegaly (7) | 80 | To PD20 (diastolic)  (0.5 mg/500 mL) | 1.0  0.3 |
| Jespersen 1988 [79] | 3 groups/incremental | CRF (not dialyzed, 8) | Ad libitum | To PD20 (diastolic) (mdn 9.7 ng/kg/min, IQR 5.9-15.2) | 4.3 |
|  |  | CRF (dialyzed, 11) |  |  | 3.0 |
|  |  | Control (14) |  |  | 2.9 |
| Kono 1977 [88] | 1 group/fixed | Normal (5) | – | 20 ng/kg/min | 2.2 |
| Lottermoser 2003 [93] | 1 group/incremental | Healthy (9) | 150-180 | 10 ng/kg/min | 7.4 |
| McCaa 1973 [100] | 3 groups/incremental | Normal  Anephric  Kidney allograft | 12 g (5), 20mEq (5) | 2 ng/kg/min until 20 mm HG (diastolic) increase | 5.9  0.86  6.4 |
| Mediskou 2011 [104] | 2 groups/incremental | Hyperprolactinemic women (20)  Healthy women (20) | 150 | 6 ng/kg/min | 2.7  Positive (graph) |
| Menard 1991 [105] | 1 group/incremental | Normal men (6) | Ad libitum | 4 ng/kg/min | 2.1 |
| Mendelsohn 1972 [106] | 2 groups/fixed | Hypertensive (17)  Normotensive (8) | 100  10  100  10 | 100 ng/min | 1.9  1.5  1.8  1.3 |
| Oelkers 1975 [118] | 1 group/incremental, sustained, incremental sequence | Normal (5) | – | Sequence:  Incremental to 12 ng/kg/min (6 h) Sustained 2 ng/kg/min for 66 h Incremental to 16 ng/kg/min (6 h) | Graphs  DR increase 4.6 Enhanced DR |
| Ozono 1996 [123] | 2 groups/incremental | Japanese subjects  Modulating eHTN (6)  Nonmodulating eHTN (9) | 250  10  250  10 | 3 ng/kg/min (high Na)  3 ng/kg/mL (low Na)  3 ng/kg/min (high Na)  3 ng/kg/mL (low Na) | Graphs:  Modest response  Greatest response  Modest response  Modest response |
| Price 1999 [126] | 3 groups/fixed | Healthy control (25)  Hypertension (137)  Hypertension, type II diabetes (42) | 10 mmol (low Na)  200 mmol (high Na) | 3 ng/kg/min | 5.3  2.5  1.9 |
| Sasaki 1983 [133] | 2 groups/incremental | Healthy control (10)  Shy-Drager syndrome (7) |  | 2.5-10 ng/kg/min | Positive (graph)  Mixed (graph) |
| Saxena 2010 [134] | 2 groups/fixed | Postpartum women (≥ 8 mo)  Normotensive pregnancy (15)  Hypertensive pregnancy (10) | 250  10  250  10 | 3 ng/kg/min (high Na)  3 ng/kg/min (low Na)  3 ng/kg/min (high Na)  3 ng/kg/min (low Na) | 4.2  2.5  5.2  3.9 |
| Schaison 1980 [136] | 1 group/target | 21-hydroxylase-deficient congenital adrenal hyperplasia, hydrocortisone-treated (4) | 200 | To PD20/10 (systolic/diastolic) (average 12 ng/kg/min; low Na) | Positive (graph) |
| Schlaich 2002 [137] | 1 group/incremental | Normotensive no FH (60)  Normotensive FH HTN (28) | Ad libitum +5 g NaCl/d | 3 ng/kg/min  3 ng/kg/min | 1.9  1.8 |
| Slaton 1967 [143] | 1 group/ | Autonomic insufficiency (5) | – | 4.0 to 9.0 ng/kg/min | 0.36-2.7 |
| Spark 1969 [148] | 2 groups/target | 1° aldosteronism, adenoma (8)  2° aldosteronism (8) | 120 | To PD10 (diastolic) | 1.9 (rate)  0.93 (rate) |
| Takeda 1980 [154] | 3 groups/fixed | Normotensive young [20-35 y] (10)  Normotensive middle aged [41-56 y] (9)  Normotensive old [66-73 y] (11) | 25 (low) | 10 ng/kg/min | 1.9  1.8  2.0 |
| Vierhapper 1983 [165] | 1 group/fixed | Healthy (6) | Ad libitum +3 g NaCl/d | 20 ng/kg/min (after Na load) | 2.3 |
| Vos 1994 [167] | 1 group/incremental | Healthy (7) high Na + enalapril 5 d prior | 340 | 8 pmol/kg/min | 3.5 |
| Witzgall 1985 [177] | 3 groups/incremental | Normotensive (7)  Essential hypertension (10)  Primary aldosteronism (10) | 150-200 mmol | 2 to 4 ng/kg/min | Positive (graph) |
| Woods 1974 [179] | 2 groups/incremental | Normotensive (6)  Nephrectomy (10)  Renal Failure (6) | 34 | +2 ng/kg/min to PD20 (diastolic) | 5.9  No change  1.8 |
| Yamamoto 1975 [180] | 5 groups/fixed | Normotensive (5)  Conn syndrome (5)  Renovascular HTN (4)  eHTN, low renin (11)  eHTN, normal/high renin (9) | 170-200 | 10 ng/kg/min | 1.4  1.4  1.4  1.5  1.7 |
| ATII, angiotensin II infusion; CRF, chronic renal failure; DR, dose response/responsive; eHTN, essential hypertension; FH, family history; HTN, hypertension/hypertensive; Na, sodium intake; NE, norepinephrine; PD10, dose of angiotensin II required to increase pressure by 10 mm Hg; PD20, dose of angiotensin II required to increase pressure by 20 mm Hg; RHD, rheumatic heart disease.  a Target, dose was adjusted to achieve a fixed pressor response (increase in SBP, DBP, or MAP); fixed dose, each subject in a group received the same dose; incremental, each subject received sequential incremental doses.  b For studies using incremental dose administration, only the dose resulting in the maximal aldosterone response is shown. In most cases, this was also the maximum dose administered.  c In most cases, response (angiotensin II infusion/baseline) was calculated post hoc for this review.  d Aldosterone response was greater before hyperparathyroidectomy than after or than in the control group.  e In modulating hypertensin, the renal and adrenal responses to angiotensin II decrease with increasing sodium intake. Mean absolute increase in aldosterone was greater in the modulating group than in the nonmodulating group. | | | | | | |

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