

Clinical Trials of Guaiacol in Adult Polyglucosan Body Disease Patients

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The FDA-approved food additive Guaiacol (CAS 90-05-1) was discovered as a drug candidate for Adult Polyglucosan Body Disease (APBD) by high throughput screening (HTS), and was confirmed in a mouse model of the disease (*Gbe1^{ys/ys}*) homozygous for the human mutation in *Gbe1*, p.Y329S. In these mouse studies, Guaiacol restored the significantly shorter lifespan of the *Gbe1^{ys/ys}* APBD modeling mice to normal levels, without any adverse effects. On the contrary, Guaiacol even corrected penile prolapse in aged *Gbe1^{ys/ys}* male mice, a urologic problem which perhaps could be related to other urologic problems found in patients. These results motivate us to initiate a phase 1-2 clinical trial to explore the therapeutic potential of Guaiacol in APBD patients.

Patients. Because of a limited patient population, we plan this trial as an open label prospective study on 17 Israeli APBD patients.

Inclusion/exclusion criteria. Diagnosis of APBD must be biochemically and genetically confirmed. Patients will be cognitively fit for informed consent. The inclusion criteria are: Unremarkable CBC, complete biochemistry, urinalysis, ECG, abdominal US.

Prospective testing. All patients will have a pre- and every 3-months on-trial clinical physical and neurological examination, CBC, complete biochemistry, urinalysis, ECG. All patients will have pre- and every 6-months 6-min walk test, EDSS and Spastic Paraplegia Rating Scale forms, orthostatic hypotension and R-R interval testing. All patients will have a pre- and yearly on-trial peripheral nerve conduction study and head MRI. All tests will be conducted until 3, objectively determined, consecutive deteriorations are recorded. The entire trial is expected to last a few years.

Safety. While No-observed-adverse-effect level (NOAEL) has not been rigorously determined, the lowest level in which adverse effects start to show in mice (N=7) is 175 mg/kg administered once sub-cutaneously(1). In our hands, this level did not show any adverse effects in mice, administered both orally and subcutaneously (N=6).

Efficacy. We don't have data, both in mice and in humans, on serum levels correlating with an effective Guaiacol dose. The only efficacy data available to us are that in humans Guaiacol was effective already at 0.03 mg/kg(2) and in mice at 22.5 mg/kg (N=6, equivalent to 1.8 mg/kg in human, our unpublished data), both administered orally.

Pharmacokinetics The only study in which Guaiacol levels in the blood were determined was a pharmacokinetic study, not addressing efficacy(3). In that study 32 mg (0.4 mg/kg, assuming average weight is 80 kg) were administered orally to N=8 men. After 30 min, Guaiacol level in the serum was < 0.04 mg/l. The following pharmacokinetic data were obtained for Guaiacol's metabolites Glucuronide and Guaiacol-Sulfate, but not for non-conjugated Guaiacol:

	C _{max} (mg/l)	t _{1/2} (h)	AUC (h*mg/l)	C _p /F (l/h)	V _{area} /F (l)
Glucuronide	0.91 ± 0.38	2.1 ± 0.6	0.97 ± 0.22	33 ± 8	100 ± 24
Sulfate	0.22 ± 0.09	2.5 ± 0.6	0.30 ± 0.13	108 ± 46	396 ± 170

References

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