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REVIEW ARTICLE

Two Decades-Long Journey from Riluzole to Edaravone: Revisiting the Clinical Pharmacokinetics of the Only Two Amyotrophic Lateral Sclerosis Therapeutics

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Abstract The recent approval of edaravone has provided an intravenous option to treat amyotrophic lateral sclerosis (ALS) in addition to the existing oral agent, riluzole. The present work was primarily undertaken to provide a comprehensive clinical pharmacokinetic summary of the two approved ALS therapeutics. The key objectives of the review were to (i) tabulate the clinical pharmacokinetics of riluzole and edaravone with emphasis on absorption, distribution, metabolism and excretion (ADME) properties; (ii) provide a comparative scenario of the pharmacokinetics of the two drugs wherever possible; and (iii) provide perspectives and introspection on the gathered clinical pharmacokinetic data of the two drugs with appropriate conjectures to quench scientific curiosity. Based on this review, the following key highlights were deduced: (i) as a result of both presystemic metabolism and polymorphic hepatic cytochrome P450 (CYP) metabolism, the oral drug riluzole exhibited more inter-subject variability than that of intravenous edaravone; (ii) using various parameters for comparison, including the published intravenous data for riluzole, it was apparent that edaravone was achieving the desired systemic concentrations to possibly drive the local brain concentrations for its efficacy in ALS patients with lesser variability than riluzole; (iii) using scientific conjectures, it was deduced that the availability of intravenous riluzole may not be beneficial in therapy due to its fast systemic clearance; (iv) on the contrary, however, there appeared to be an opportunity for the development of an oral dosage form of edaravone, which may potentially benefit the therapy option for ALS patients by avoiding hospitalization costs; and (v) because of the existence of pharmaco-resistance for the brain entry in ALS patients, it appeared prudent to consider combination strategies of edaravone and/or riluzole with suitable P-glycoprotein efflux-blocking drugs to gain more favorable outcomes in ALS patients.

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Key Points

Recent approval of intravenous edaravone for the treatment of amyotrophic lateral sclerosis (ALS) has ended a two-decade-long despair in the field after the first approval of oral riluzole.

This work critically reviews the clinical pharmacokinetics of the only two approved agents for ALS, including a comparative section on covariates affecting the disposition of riluzole and edaravone.

Riluzole pharmacokinetics were susceptible to a high degree of variability due to a multitude of factors such as presystemic metabolism, polymorphic hepatic metabolism, and extra-hepatic metabolism and, in addition, the influence of P-glycoprotein (P-gp) efflux pump at the blood–brain barrier (BBB) may have caused variable uptake of the drug into brain.

Both due to avoidance of oral bioavailability issues and involvement of only the glucuronidation pathway (i.e., non-polymorphic uridine 5'-diphospho-glucuronosyltransferases [UGTs]) and less of an influence of P-gp efflux at the BBB, intravenous edaravone may have less variable brain transport.

Intravenous edaravone achieved higher systemic levels to possibly drive the brain penetration for its efficacy in ALS patients with a lesser degree of variability than oral riluzole. However, a head-to-head comparative trial of edaravone versus riluzole in ALS patients is yet to be reported.

1 Introduction

In 1869, Charcot and Joffroy described amyotrophic lateral sclerosis (ALS), for the first time, as a lethal neurodegenerative disorder characterized by gradual loss of the motor neurons in the brain stem and spinal cord, resulting in the atrophy of voluntary skeletal muscles and ultimately leading to paralysis [1]. ALS is also commonly known as 'Lou Gehrig's disease'. In this disease, the loss of lower motor neurons innervating the skeletal muscle results in weakness, atrophy, fibrillations, decreased muscle tone, loss of tendon reflexes, and fasciculations, whereas loss of upper motor neurons is associated with increased spasticity, abnormal extensor reflexes, and hyperactive reflexes [2–7]. ALS patients also show various other symptoms, namely cramps, dysarthria, thinned lips, weakness, and problems swallowing resulting in regurgitation, thus increasing the prevalence of aspiration pneumonia [3, 8, 9]. However, the motor neurons controlling the extraocular and sphincter muscles as well as sensory and autonomic neurons of the viscera are not affected in this disorder [2, 10, 11]. Unfortunately, the respiratory muscles are affected, resulting in the death of most patients due to respiratory failure within 2–5 years after diagnosis [2, 12–14]. The average survival rate is only 10%, with a life expectancy of 10 years [3, 4].

Although the disease has been known and well-characterized for several decades now, there is still a dearth in the drug approvals for ALS. The primary reason for the lack of treatment options might be attributed to the complex etiology of the disease. Familial ALS accounts for about 5–10% of total ALS cases, where at least 13 genes and loci majorly contribute to pathology. Of these, mutations in the *SOD1* (superoxide dismutase 1) gene have been extensively studied as *SOD1* mutations account for approximately 20% of cases of familial ALS and 5% of sporadic ALS [15]. Unfortunately, the exact mechanisms underlying the *SOD1*-mediated disease progression is still unclear. However, the discovery of the first transgenic *SOD1G93A* mouse model in 1993, which closely mimics human familial ALS pathology, was a breakthrough in the field of ALS research that opened opportunities for preclinical research [16].

Despite of all these advancements, to date there are only two approved drugs, namely riluzole and edaravone, for the treatment of ALS (Fig. 1). The development of riluzole started in late 1980s as a free radical scavenger for stroke therapy [17]. However, it has not been approved for treatment of stroke in the USA or Europe. Thereafter, it was repositioned for ALS therapy, but failed in many clinical trials prior to its final approval by the US Food and Drug Administration (FDA) in 1995 [17]. Following the approval of riluzole, more than 60 drugs belonging to various therapeutic categories, namely anti-glutaminergic, anti-inflammatory, anti-oxidative, neuroprotective, neurotrophic agents, and colony-stimulating factor 1R inhibitors, have been tried for ALS therapy to date, but none with success [18]. Thereafter, in 2001, edaravone obtained market approval for the management of stroke in Japan. The edaravone clinical trials for ALS started in 2011 and culminated in Japanese approval for ALS therapy in 2015. In 2017, edaravone got US FDA approval for ALS [17]. The two approved agents for ALS have interesting mechanism of actions. Riluzole acts by inhibiting the glutaminergic transmission and subsequently decreasing the glutamate-mediated excitotoxicity [19]. In vivo studies for

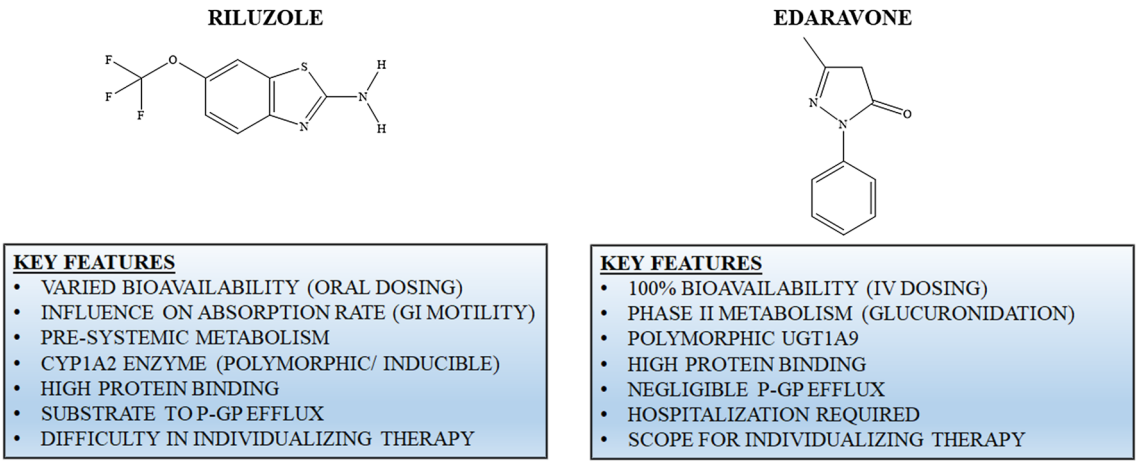

Fig. 1 Chemical structure and key features of riluzole and edaravone. *CYP* cytochrome P450, *IV* intravenous, *P-GP* P-glycoprotein, *UGT* uridine 5′-diphospho-glucuronosyltransferase

riluzole showed inhibition of the release of glutamic acid from cultured neurons, brain slices, and corticostriatal neurons. It also blocks some of the postsynaptic effects of glutamic acid by non-competitive blockade of *N*-methyl-D-aspartate (NMDA) receptors [19]. Furthermore, riluzole possesses free radical scavenging activity [19]. Edaravone primarily acts by scavenging the hydoxyl, peroxyl, and superoxide radicals that mediate neuronal and vascular damage [17, 19, 20]. The mechanism of absorption and transport of riluzole and edravone to reach the blood–brain barrier (BBB) is depicted in Fig. 2.

2 Scope

Although many studies on the pharmacokinetic aspects of riluzole have been reported recently, no review article has been published since 1997. Also, a comprehensive review

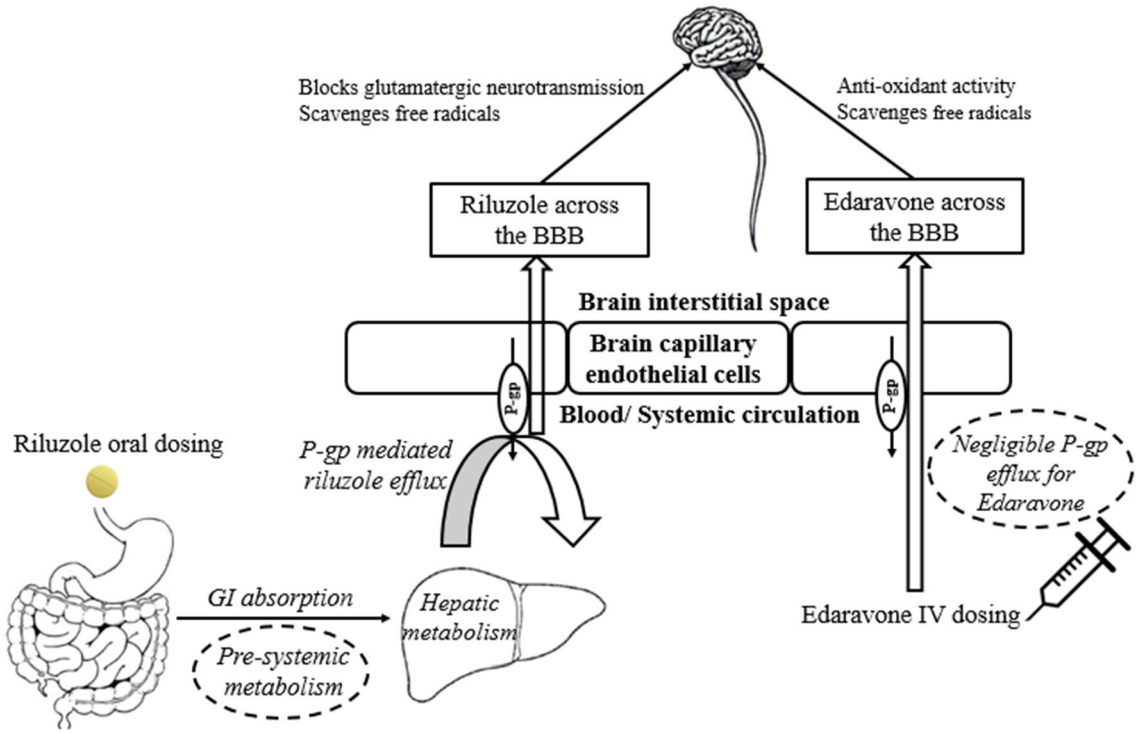

Fig. 2 Schematic representation of the mechanism of action and transport of riluzole and edaravone across the blood–brain barrier from the site of drug administration. *BBB* blood–brain barrier, *GI* gastrointestinal, *IV* intravenous, *P-gp* P-glycoprotein

Table 1 Summary of study design and pharmacokinetic data of riluzole in clinical studies

Study particulars: subjects/design	PK data							Remarks
	Type	C_{max} (μg/mL)	t_{max} (h)	$t_{½}$ (h)	AUC (μg·h/mL)	CL/*F* (L/h)	V_d (L/kg)	
Le Liboux et al. [33]								Absolute bioavailability was 60%, elimination was independent of the dose. PK parameters showed some intra-individual variation and high-fat diet reduced the rate and extent of absorption. Steady-state trough concentration with 75 mg tid was significantly higher than 50 mg bid with no impact on AUC levels
Study 1 (absolute oral bioavailability study): HV (16 M), open, randomized, crossover design. 50 mg IV dose, followed by 2 oral doses of 100 mg, with a washout period of 7 days between each period	Study 1							
	100 mg	0.32 ± 0.20	1.1 ± 0.5	8.0 ± 2.6	1.33 ± 0.57	88.08 ± 34.8	13.79 ± 5.56	
	100 mg (1 week later)	0.43 ± 0.24	1.1 ± 0.8	7.3 ± 1.6	1.41 ± 0.61	79.8 ± 24.54	11.73 ± 3.56	
	50 mg IV	0.58 ± 0.14		5.9 ± 2.1	1.08 ± 0.20	47.64 ± 8.4	5.65 ± 2.17	
Study 2 (tolerability study): HV (12 M), randomized, double-blind, placebo-controlled design. Group 1: 25, 75, 150, and 250 mg; Group B: 50, 100, 200, and 300 mg. Washout period of 7 days between each dose level	Study 2							
	25 mg	0.09 ± 0.04	1.0[a]	9.7 ± 1.9	0.57 ± 0.18			
	50 mg	0.21 ± 0.09	1.4[a]	14.0 ± 6.3	1.34 ± 0.43			
	75 mg	0.25 ± 0.14	0.9[a]	10.6 ± 2.0	1.34 ± 0.56			
	100 mg	0.43 ± 0.24	1.4[a]	11.8 ± 3.0	2.54 ± 1.62			
	150 mg	0.56 ± 0.26	1.1[a]	10.6 ± 2.5	2.53 ± 1.03			
	200 mg	1.12 ± 0.76	1.5[a]	10.4 ± 3.3	5.24 ± 2.54			
	250 mg	0.89 ± 0.33	1.3[a]	9.4 ± 2.0	3.89 ± 1.50			
	300 mg	1.61 ± 0.67	1.3[a]	9.2 ± 2.9	7.55 ± 3.36			
Study 3 (food effect): HV (16 M), open, randomized, crossover design. Single 100 mg oral dose, fasted and after high-fat breakfast with a washout period of 7 days between each treatment	Study 3							
	100 mg (fasting)	0.39 ± 0.19	0.8[a]	7.1 ± 1.7	1.27 ± 0.63			
	100 mg (fed)	0.22 ± 0.14	2.0[a]	6.6 ± 1.5	1.05 ± 0.48			
Study 4 (multiple-dose PKs): HV (12 M), randomized, double-blind, placebo-controlled design. Single oral dose of 25, 50, or 100 mg (day 1) and then as multiple doses of 25, 50, or 100 mg bid for 10 days (days 3–13)	Study 4							
	25 mg (single dose)	0.05 ± 0.02	1.1 ± 0.7	5.2 ± 1.2	0.21 ± 0.09			
	50 mg (single dose)	0.18 ± 0.12	0.9 ± 0.5	6.4 ± 1.9	0.54 ± 0.27			
	100 mg (single dose)	0.28 ± 0.13	1.6 ± 1.1	5.8 ± 1.5	1.20 ± 0.6			
	25 mg bid	0.07 ± 0.03	0.8 ± 0.3	9.2 ± 3.8	0.30 ± 0.12			
	50 mg bid	0.17 ± 0.07	0.8 ± 0.5	14.7 ± 4.9	0.65 ± 0.28			
	100 mg bid	0.36 ± 0.17	1.3 ± 0.4	13.0 ± 4.3	1.48 ± 0.74			
Study 5 (multiple divided dose PKs): HV (12 M), randomized, double-blind, placebo-controlled design. 150 mg dose administered either as 75 mg bid or 50 mg tid for 7 days with a washout period of 7 days	Study 5							
	50 mg tid	0.18 ± 0.13	1.0[a]		3.61 ± 1.59			
	75 mg tid	0.30 ± 0.25	1.5[a]		4.02 ± 2.50			
Le Liboux et al. [35]								$t_{½}$ was found to be significantly different in between elderly and young subjects with no impact on other PK parameters
N = 36 HV (elderly subjects: 9 M, 9 F; and young subjects: 9 M, 9 F), open-label, non-randomized, parallel-group, repeat-dose study	Elderly male	0.28 ± 0.09	0.75[a]	42.08 ± 11.31	1.01 ± 0.30	52.42 ± 19.31		
	Elderly female	0.26 ± 0.15	0.75[a]	38.52 ± 5.55	1.05 ± 0.50	66.22 ± 37.24		
	Young male	0.20 ± 0.10	0.75[a]	49.33 ± 11.08	0.86 ± 0.43	65.70 ± 26.14		
	Young female	0.29 ± 0.16	0.50[a]	48.80 ± 11.49	0.88 ± 0.52	76.29 ± 36.73		
Day 1–4: 50 mg film-coated tablets bid, at a 12-h interval								
Day 5: single-dose 50 mg administered 2 h before breakfast								

Table 1 continued

Study particulars: subjects/design	PK data							Remarks
	Type	C_{max} (μg/mL)	t_{max} (h)	$t_{½}$ (h)	AUC (μg·h/mL)	CL/*F* (L/h)	V_d (L/kg)	
Groeneveld et al. [62] *N* = 169 ALS patients administered 50 mg riluzole bid		0.23 ± 0.01			3.41 ± 0.22			The plasma exposure based on AUC levels was significantly higher in ALS patients as than in healthy subjects in a similar dosing regimen
Abbara et al. [37] *N* = 13 (4 M, 9 F) patients with skeletal muscle atrophy. 50 mg riluzole od		0.37 ± 0.06	1[a]	9.8 ± 1.3	2.26 ± 0.44	22.15[b]	10.67 ± 1.93	The plasma exposure based on AUC levels was similar in skeletal muscle atrophy subjects for qid dose was similar to that of ALS patients receiving riluzole 50 mg bid
Chow et al. [38] *N* = 33 patients with SCI. Riluzole 50 mg dosed by oral or nasogastric administration every 12 h, starting within 12 h of injury for 28 doses	Day 3 Day 14	0.13 ± 0.01 0.08 ± 0.02		11.91 ± 2.18 10.61 ± 2.23	0.98 ± 0.11 0.52 ± 0.09	49.47 ± 7.77 106.20 ± 19.80	6.86 ± 0.91 15.58 ± 2.63	Riluzole exposure in SCI patients were lower than ALS patients due to high clearance and larger V_d in SCI patients

Data expressed as mean ± standard deviation for all parameters unless indicated

ALS amyotrophic lateral sclerosis, *AUC* area under the plasma concentration–time curve, *bid* twice daily, *CL/F* total body clearance, C_{max} maximum plasma concentration, *F* female, *HV* healthy volunteers, *IV* intravenous, *M* male, *od* once daily, *PK* pharmacokinetic, *qid* four times daily, *SCI* spinal cord injury, $t_{½}$ half-life, *tid* twice daily, t_{max} time to reach maximum plasma concentration, V_d volume of distribution

[a]Data expressed as median

[b]Data expressed as mean

on the pharmacokinetics of edaravone is not available. The current review is designed to provide ready accessibility on the clinical pharmacokinetics of these two drugs. The key objectives of this review are to (i) collate and describe the pharmacokinetic data of riluzole and edaravone; (ii) establish a comparison, wherever possible, between the clinical pharmacokinetics of riluzole and edaravone; and (iii) provide a broad perspective on relevant clinical pharmacology considerations during clinical therapy with riluzole and edaravone using the reviewed literature information. The clinical pharmacokinetic data of riluzole and edaravone are tabulated in Tables 1 and 2, respectively. Figure 1 shows the key features of the two drugs along with the respective chemical structures. Figure 2 is a schematic tracking of riluzole (oral) versus edaravone (intravenous) from the site of drug administration reaching the brain, where pharmacological action of the two drugs is expected to occur.

The literature review was performed using the PUBMED® (NCBI [National Center for Biotechnology Information] 2016), SCIFINDER®, and Google Scholar databases with specific keywords such as riluzole, edaravone, preclinical, clinical, pharmacokinetics, absorption, distribution, metabolism, excretion, bioavailability, disposition, transporter, drug–drug interaction, and human to collect the related full-length articles and abstracts.

3 Clinical Pharmacokinetics of Riluzole

3.1 Absorption and Bioavailability

Riluzole did not exhibit any bioavailability issues following oral administration in humans. In an oral mass balance study, an almost complete absorption was noted (> 90%) with an absolute bioavailability of about 60% [21]. Riluzole is rapidly absorbed after oral administration with a time to reach maximum plasma concentration (t_{max}) of 1–1.5 h across the studied dose ranges [22]. The exposure was found to be linear over a dose range of 25–300 mg, given every 12 h [23].

3.2 Distribution

Riluzole showed good tissue distribution with a volume of distribution (V_d) of approximately 3.4 L/kg. It exhibited a protein binding of 96% in human plasma, with primary affinity towards albumin and lipoproteins [24].

3.3 Metabolism

Riluzole exhibited a complex metabolism consisting of phase I via cytochrome P450 (CYP) enzymes and phase II conjugation reactions [22]. The phase I metabolic pathways involved aromatic hydroxylation occurring at the trifluoromethoxy benzene moiety of the benzothiazole ring

Table 2 Summary of study design and pharmacokinetic data of edaravone in clinical studies

Study particulars: subjects/design	PK data						Remarks
	Type	C_{max} (μg/mL)	t_{max} (h)	$t_{½}$ (h)	AUC (μg·h/mL)	CL/*F* (L/h)	V_d (L/kg)	
Li et al. [28]								Plasma exposure of edaravone was found to increase linearly with the increasing dose with no effect on drug elimination
N = 30 HV (15 M, 15 F); single-center, open-label	20 mg	1.60 ± 0.38		2.34 ± 0.69	3.79 ± 1.40[a]	6.0 ± 1.8	19.3 ± 7.3	
IV infusion: group 1: 20 mg single dose; group 2: 30 mg on days 1–4 and twice on day 5; group 3: 60 mg single dose	30 mg single dose	2.38 ± 0.32		2.25 ± 0.42	5.29 ± 0.98[a]	6.0 ± 1.2	18.5 ± 2.6	
	30 mg repeated dose	2.48 ± 0.48		2.52 ± 0.51	5.24 ± 0.94[a]	6.0 ± 1.2	21.0 ± 4.1	
	60 mg	4.54 ± 0.90		2.57 ± 0.32	11.59 ± 3.62[a]	5.4 ± 1.8	20.7 ± 6.5	
Kaste et al. [39]								Dose linearity was observed in this study and edaravone concentrations remained unaffected by renal function or other patient parameters
N = 18 stroke patients in a multicenter, double-blind, placebo-controlled study	Cohort 1							
	Edaravone	0.39[b]						
Cohort 1: loading dose of 0.08 mg/kg followed by a continuous infusion of 0.2 mg/kg/h for 72 h	Glucuronide metabolite	5.68[b]						
	Sulfate metabolite	12.09[b]						
Cohort 2: loading dose of 0.16 mg/kg followed by a continuous infusion of 0.4 mg/kg/h for 72 h	Cohort 2							
	Edaravone	1.60[b]						
	Glucuronide metabolite	8.50[b]						
	Sulfate metabolite	14.62[b]						
Nakamaru et al. [34]								V_d in Caucasian subjects was 26% higher than in Japanese subjects with no impact on other PK parameters
N = 1000 Japanese and Caucasian subjects, simulated exposure following 14 days daily infusion for 1 h at 30, 60, and 120 mg doses	Japanese							
	Day 1							
	30 mg	0.47 ± 0.05			0.6 ± 0.09			
	60 mg	1.05 ± 0.11			1.37 ± 0.19			
	120 mg	2.29 ± 0.25			3.14 ± 0.46			
	Day 14							
	30 mg	0.47 ± 0.05			0.6 ± 0.09			
	60 mg	1.05 ± 0.11			1.37 ± 0.19			
	120 mg	2.30 ± 0.25			3.16 ± 0.46			
	Caucasian							
	Day 1							
	30 mg	0.50 ± 0.05			0.6 ± 0.09			
	60 mg	1.05 ± 0.12			1.36 ± 0.19			
	120 mg	2.30 ± 0.25			3.13 ± 0.46			
	Day 14							
	30 mg	0.47 ± 0.05			0.6 ± 0.09			
	60 mg	1.05 ± 0.12			1.37 ± 0.2			
	120 mg	2.29 ± 0.25			3.16 ± 0.47			

Data expressed as mean ± SD for all parameters unless indicated

AUC area under the plasma concentration–time curve, AUC_{∞} area under the plasma concentration–time curve from time zero to infinity, *CL/F* total body clearance, C_{max} maximum plasma concentration, *F* female, *HV* healthy volunteers, *IV* intravenous, *M* male, *PK* pharmacokinetic, *SD* standard deviation, $t_{½}$ half-life, t_{max} time to reach maximum plasma concentration, V_d volume of distribution

[a] AUC_{∞}

[b] Not SD values reported

resulting in the formation of the phenolic metabolites, namely RP 65331, RP 65110, and RP 65077 and one hydroxylamine metabolite, namely RPR 112512 [22]. The hydroxylamine metabolite thereafter conjugated with uridine diphosphate glucuronic acid [UDGP] to form *O*- and *N*-glucurono-conjugated derivatives. In summary, the phase II reaction resulted in the glucuronoconjugation of riluzole and its phenolic metabolites [22].

CYP1A2 (liver), CYP1A1 (extrahepatic), and the glucuronotransferase isoenzyme uridine 5′-diphospho-glucuronosyltransferase [UGT]-HP4 are the primary drug-metabolizing enzymes involved in the biotransformation of riluzole [22]. There appears to be no involvement of other polymorphic CYP450 enzymes (namely CYP2D6, CYP2C8/9, and CYP2C19) or the inducible isoforms CYP2E1 and CYP3A in the metabolism of riluzole. CYPIA2-mediated hydroxylation of the primary amine group of riluzole resulted in the formation of *N*-hydroxyriluzole, which undergoes subsequent glucuronidation [23]. CYP1A1 mediated the formation of hydroxylamine metabolite (RPR 112512), phenolic metabolites RP 65077 and RP 65110, and the *O*-dealkylated compound RPR 109792. The potential involvement of CYP1A1-mediated metabolism indicated an extrahepatic metabolism in the lungs, which is known to express this isoenzyme predominantly and is not found in the liver [22]. A study by van Kan et al. [25] in 30 ALS patients suggested that the 37% observed variability in riluzole efficacy is modulated by CYP1A2-mediated polymorphism [25]. The systemic circulatory levels encompassed unchanged riluzole, low levels of the hydroxyl metabolites (namely RP 65331, RP 65110, and RP 65077), and the two glucurono-conjugate derivatives [22].

In vitro studies in human liver microsomes have confirmed the formation of the labile hydroxylamine metabolite of riluzole (RPR 112512), which then rapidly undergoes glucuronoconjugation to form the glucuronide metabolite. This may possibly explain the absence of circulatory levels of RPR 112512 in the biological samples [22].

The clearance of riluzole exhibited a large inter-individual variability and was initially attributed to genetic polymorphism with the polymorphic enzyme UGT1A1. However, a clinical study of riluzole in 131 ALS patients showed that the *UGT1A1**28 genotype was not associated with trough or peak serum concentrations of riluzole [26]. Thus, it may be presumed that other isoforms of the UGT family may play a role in the riluzole glucuronidation pathway [26].

3.4 Excretion

The apparent plasma clearance of riluzole following single oral doses of 25–300 mg ranged from 41.9 to 69.8 L/h [22]. Riluzole exhibited an intermediate hepatic extraction ratio of 0.67, thus suggesting that the hepatic clearance of riluzole will likely be affected by factors such as hepatic blood flow, liver intrinsic enzyme activity, and fraction unbound [22]. Riluzole and its metabolites are primarily cleared by renal elimination and minimally by the fecal route [23]. The urine showed 91% of the radioactivity of the administered dose of riluzole within the first 24 h; 85% of the radioactivity appeared as glucuronide metabolites and only 2% as unchanged drug. Approximately 5% of the administered oral dose is eliminated in the feces [24]. Riluzole also exhibited extensive enterohepatic circulation, as evident from the biliary excretion of about 50% of the administered dose and an average of 74% of the biliary radioactivity getting reabsorbed. Thus, the biliary excretory pathway of riluzole may be affected in hepatic impaired patients. The average elimination half-life ($t_{½}$) of riluzole was 12 h and was independent of the dose [22].

In a well-controlled clinical study in terms of diet, smoking habits, and hepatic function involving 21 ALS patients dosed with riluzole 50 mg twice daily, very high inter-individual variation (coefficient of variation = 74%) was observed in the clearance. In contrast, however, the intra-individual variation was observed to be minimal, suggesting that individual dosage adjustments may not be necessary in ALS patients due to variable population clearance of riluzole [21]. The variable clearance resulted in 30- to 50-fold differences in trough and peak concentrations of riluzole and might be a probable reason for the variable life expectancy of ALS patients [21]. It was suggested that phenotypic variation of CYP1A2 activity may be a contributor, but this has not been investigated [21].

A population pharmacokinetic study of riluzole in 100 ALS patients showed significant inter-individual variability in plasma clearance (51.4%), which was higher than intra-individual variability (28%), suggesting that riluzole clearance would remain controlled during the therapy in a given patient [27]. The clearance was found to be 26 L/h and V_d was 5 L/kg. The population model also revealed that clearance of riluzole was not affected by dosage (25–100 mg twice daily), treatment duration (up to 10 months), age, and renal function. However, the clearance was affected to a greater degree by the sex and smoking covariates and to a lesser by degree hepatic function [27].

4 Clinical Pharmacokinetics of Edaravone

4.1 Absorption and Bioavailability

Since edaravone is an intravenous therapy to manage ALS, there is no oral dosage formulation of the drug used in

clinical therapy. Hence, issues that typically hinder oral absorption and bioavailability do not pose a challenge for edaravone.

4.2 Intravenous Pharmacokinetics

Li et al. [28] demonstrated dose linearity in the pharmacokinetics of edaravone following single- and multiple-dose intravenous administration in healthy Chinese subjects. The plasma exposure (area under the plasma concentration–time curve [AUC] levels) following 30 and 60 mg doses was 1.4 and three times higher than the 20 mg dose [28]. The mean plasma exposure following multiple dosing twice daily for 5 days with the 30 mg dose was the same as that of single-dose exposure, suggesting no accumulation of edaravone [28]. Wei and Xiao [29] demonstrated that coadministration of low-molecular weight heparin calcium injection (5000 U, twice daily, hypodermic injection, continuously used for 5 days) significantly ($p < 0.01$) increased the plasma concentration of edaravone (30 mg intravenous infusion for 14 days).

4.3 Distribution

Edaravone exhibited high V_d of 20 L/kg and high human plasma protein binding of greater than 92%, mainly to albumin [28, 30]. Preclinical studies showed feto-placental transfer of edaravone with a higher level of radioactivity in the intestine, kidney, liver, and brain of the fetus, where 44 and 23% of the radioactivity in the fetus consists of sulfate and glucuronide metabolites of edaravone [31].

4.4 Metabolism

Glucuronide conjugation is the primary pathway for edaravone metabolism. Ma et al. [32] observed that edaravone glucuronidation in human liver and kidney microsomes exhibited biphasic kinetics. The intrinsic clearance of glucuronidation at the high-affinity phase and low-affinity phase were found to be 8.4 ± 3.3 and 1.3 ± 0.2 μL/min/mg, respectively, for human liver microsomes and were 45.3 ± 8.2 and 1.8 ± 0.1 μL/min/mg, respectively, for human kidney microsomes [32]. Eight UGTs (UGT1A1, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B17) were found to contribute to the production of a significant amount of glucuronide metabolite [32]. Among them, highest activity was exhibited by UGT1A9 followed by UGT2B17 and UGT1A7. An inhibition study using propofol (UGT1A9-specific inhibitor) reduced edaravone glucuronidation in human liver and kidney microsomes [32].

4.5 Excretion

The $t_{½}$ of edaravone was found to be 2.5 h both in a single- as well as multiple-dosing regimen, thus suggesting rapid elimination [28]. Approximately, 70% of the dose was excreted as glucuronide-conjugated metabolite in human urine. Also, the clearance did not change following multiple dosing, which resulted in constant exposure after repeated drug administration [28]. Preclinical studies showed high levels of radioactivity of sulfate metabolite of edaravone as well as parent edaravone in the milk of rats, thus suggesting further post-partum fetal exposure [31].

5 Influence of Covariates on Pharmacokinetics of Riluzole and Edaravone

5.1 Food Effect

A food effect has been reported for riluzole. Following a high-fat meal, there was a significant delay in the occurrence of t_{max} (2 h in fed vs. 0.8 h in fasted) and the maximum plasma concentration (C_{max}) was lower after food (216 ng/mL) than in fasted subjects (387 ng/mL). The extent of absorption was reduced with the food intake (AUC = 1047 vs. 1269 ng·h/mL) [33]. Because the approved therapy for edaravone is an intravenous formulation, the consequences of food have no bearing for dosage adjustment. If an oral formulation of edaravone is introduced in the future, a formal food effect would become necessary.

5.2 Effect of Race

As riluzole exhibits higher inter-individual variability (within a given race, for instance) in drug exposure due to the occurrence of polymorphism in its metabolism, it would be difficult to consider race as a covariate. However, with respect to edaravone, a population pharmacokinetic model by Nakamura et al. [34] that included five studies in Caucasian and Japanese subjects showed race as an important covariate. In particular, the V_d in Caucasian subjects was 26% higher than in the Japanese subjects [34]. Interestingly, the difference in the pharmacokinetic profile was not attributable to age, sex, or body weight [34].

5.3 Effect of Sex

A population pharmacokinetic study by Bruno et al. (1997) showed that the clearance of riluzole was 32% lower in women than in men, thus suggesting sex as a covariate that may affect the pharmacokinetics of riluzole [27]. However, in a subsequent study the pharmacokinetic profile of

riluzole was found to be similar in both sexes [35]. No sex effect in the pharmacokinetics of edavarone has been found [36].

5.4 Effect of Age

Le Liboux et al. [35] studied the effect of age on the pharmacokinetics of riluzole in healthy elderly and young subjects following repeated dosing. There was no significant difference in the pharmacokinetics of riluzole between the two age groups with the exception of the $t_{½}$, which varied with the sex as well as the age group (elderly males 42.08 h vs. young males 49.33 h and elderly females 38.52 h vs. young females 48.8 h) [35]. No data on an age effect on the pharmacokinetics of edaravone have been reported.

5.5 Protein Binding

Both riluzole and edaravone exhibited high human plasma protein binding of 96 and 92%, respectively, primarily to albumin [23, 36]. Thus, it may be presumed that any pathological condition such as malnutrition that decreases the albumin concentrations could potentially increase the plasma concentrations of riluzole and edaravone and exacerbate its pharmacological effect. The plasma profile comprising the free fraction (i.e., unbound concentrations) for either edaravone or riluzole have not been reported in ALS patients.

6 Special Population Pharmacokinetics

Pharmacokinetic studies have shown that young spinal muscular atrophy subjects when given riluzole 50 mg once a day showed comparable exposure to that seen in adult healthy volunteers or ALS patients receiving 50 mg twice daily [37]. Chow et al. [38] demonstrated that the plasma exposure (AUC) of riluzole in spinal cord injury (SCI) patients was fourfold lower than in ALS patients, which was attributed to high clearance (SCI 49.47 ± 7.77 L/h vs. ALS 25.9 ± 14.72 L/h) and larger V_d (SCI 15.58 ± 2.63 L/kg vs. ALS 5 L/kg). Furthermore, C_{max}, minimum concentration (C_{min}), and AUC from time zero to 24 h (AUC_{12}) (0.13 µg/mL, 0.05 µg/mL, and 0.9 µg·h/mL, respectively) were significantly higher on Day 3 than on Day 14 (0.08 µg/mL, 0.02 µg/mL, and 0.5 µg·h/mL, respectively). These variations were attributed to the lower clearance (49.5 vs. 106.2 L/h) and smaller V_d (6.71 vs. 15.58 L/kg) on Day 3 [27, 38].

Kaste et al. [39] developed a short treatment protocol of 72 h infusion for edaravone to overcome the long duration of treatment of twice a day infusion for 14 days. The findings of this study in acute ischemic stroke patients showed good tolerability. The plasma concentration of edaravone increased rapidly and reached the steady state within 24 h of start of infusion and remained constant until the end of intravenous infusion time of 72 h. Also, dose-linearity was observed in this treatment regimen. [39]

7 Drug–Drug Interaction Potential

Riluzole, being metabolized by CYP enzymes, is more likely to be subjected to drug–drug interactions. Furthermore, a study by Milane et al. [40] showed that riluzole is a substrate for breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp), and thus likely to be prone to transporter-mediated interaction, which could also could be a major hurdle in its brain accessibility [40].

The pharmacokinetics of edaravone are not expected to be significantly affected by inhibitors of CYP enzymes, UGTs, or major transporters. The findings from in vitro studies demonstrated that, at a clinical dose, edaravone and its metabolites are not expected to potentially inhibit CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4), UGT1A1, UGT2B7, or transporters (P-gp, BCRP, organic anion transporting polypeptide [OATP] 1B1, OATP1B3, organic anion transporter [OAT] 1, OAT3, and organic cation transporter [OCT] 2) in humans [36].

8 Discussion

The development of ALS therapeutics has been an uphill task, with many promising starts that never made it to the finish line. There was a huge time lag of 22 years between the first approval of riluzole (1995) and the recent approval of edaravone (2017). Over these 22 years, more than 60 molecules have been investigated as a possible treatment for ALS and reached various stages of clinical development phases. A recent review by Petrov et al. [18] compiled the drugs that failed in the late stages of clinical trials for ALS.

Although riluzole exhibited reasonable efficacy in this difficult to treat population, the major limitation with this therapy was the occurrence of high inter-subject variability due to many factors (Fig. 1). Hence, a common dose selection for patients in general, rather than dose individualization, may have been a factor for reduced efficacy of the drug since, if not adequately managed by the administered dose, the disease progression significantly affected the life expectancy in the diseased population. Being an oral therapy, riluzole was expected to improve convenience, reduce the cost of treatment because of no

hospitalization needed, and would support outpatient prescription of the drug. However, due to the occurrence of variable presystemic metabolism and varied oral drug absorption due to inherent gastrointestinal motility in this population, further compounded by the metabolic variation imposed by the polymorphic hepatic CYP1A2 enzyme and extra-hepatic CYP1A1 enzyme, it would have resulted in varying exposure levels of riluzole. Furthermore, the pharmacokinetic behavior of riluzole also differed significantly across the patients with different categories of central nervous system-related disorders [38]. For example, the plasma exposure (AUC levels) of riluzole in SCI patients was fourfold lower than in ALS patients, which was attributed to specific physiological factors seen in SCI patients, namely impaired gastric emptying and intestinal motility, elevated distribution resulting from hypoalbuminemia, and altered hepatic metabolism [38]. Despite the pharmacokinetic variability and metabolism-related limitation associated with riluzole resulting in variable efficacy, no fast follower approach was readily apparent to close the gap in its pharmacokinetic behavior and/or remove the polymorphic enzyme hurdle. The probable reason for the lack of successful fast follower program(s) may be the epidemiology of this disease affecting only 1–2 people per 100,000 and, therefore, the risk involved in developing another 'me-too' drug that had to demonstrate efficacy in non-responders to riluzole. Another reason may be the difficulty in identifying newer chemical scaffold(s) to get rid of metabolism-related deficiency of riluzole for creating a well-differentiated analog, and thus a fast follower strategy was perhaps not pursued.

The intravenous administration of edaravone 60 mg over a 60-min infusion (therapeutic dose) ensures the availability of the drug without oral bioavailability issues. Because of the intravenous administration of edaravone, it may be speculated that a higher proportion of the drug may cross the BBB. In a dog study, the cerebrospinal fluid (CSF) concentration of edaravone was approximately 50–65% of the plasma concentration, suggesting the likelihood of adequate exposure of edaravone in the human brain tissue to facilitate the purported free radical scavenging ability and antioxidant properties of the drug [41]. In a recent review, the overexpression of P-gp in the BBB and the impact it may have on the transport of riluzole has been discussed [42]. Hence, from the standpoint of oral dosing of riluzole, it may be speculated that it is unlikely a large plasma concentration gradient of riluzole is readily available to effectively negate the efflux capacity at the BBB because of the issues generalized in Fig. 1. On the contrary, by virtue of intravenous dosing, it may be more favorable for edaravone to overcome the efflux activity. However, as pointed out by Mohamed et al. [42], newer therapeutic options that can effectively overcome the pharmaco-resistance at the BBB need to be explored to improve the outcome in ALS patients [42]. In this context, a review of elacridar, a well-established P-gp inhibitor, has been published, providing insights and strategies to effectively use elacridar in combination to improve the brain penetration of therapeutics [43]. Apart from elacridar, other third-generation P-gp inhibitors such as tariquidar, zosuquidar, laniquidar, and ONT-093 may be considered for effective brain delivery [43]. Also, from the formulation perspective, excipients such as caprylocaproyl macrogol-8/polyoxyl-8 glycerides, polyethylene glycol (PEG) stearates, PEG fatty acid esters, polysorbates, poloxamers, sucrose monolaurate, sucrose monooleate, and chitosan-thiobutylamidine, which are reported to inhibit P-gp, may serve as a potential approach to overcome the P-gp-mediated efflux of the two agents [44, 45].

In order to provide a balanced view on the two approved therapeutics from the brain kinetics perspective, we attempted to gather some preclinical data that provided information on the brain penetration and/or distribution of the two drugs. A study by Bondì et al. [46] demonstrated that the brain distribution of riluzole was enhanced by 30% from a riluzole solid-lipid nanoparticle (SLN) formulation as compared with naïve riluzole following intraperitoneal dosing. In this study, it was also shown that the brain:-plasma ratio for riluzole SLN was 3.1 as compared with 1.6 observed for naïve riluzole dosing [46]. Milane et al. [47] observed that the brain:plasma ratios for riluzole in mdr1a (−/−) mice and mdr1a (+/+) mice were 4.6 and 2.4, suggesting potential involvement of P-gp in modulating the brain penetration of riluzole [47]. This was further confirmed by the coadministration of minocycline, which improved the brain AUC of riluzole by twofold, resulting in neuromuscular toxicity [47]. Single-dose intrathecal administration of riluzole showed significantly higher CSF levels of riluzole while maintaining lower plasma levels than those achieved through oral administration [48].

Edaravone exhibited a brain:plasma ratio of 6 following intravenous administration in rats at a dose of 3.75 mg/kg, suggesting high brain penetration [49]. The presence of borneol, which promotes brain penetration of many drugs, did not enhance the brain penetration of edaravone while improving the brain distribution of puerarin in the same study [49]. This suggested that edaravone can penetrate the BBB by itself with a low risk of P-gp efflux. Rong et al. [50] attempted to enhance the oral bioavailability of edaravone with the use of hydroxypropyl-sulfobutyl-β-cyclodextrinin, acting as both a P-gp efflux pump modulator and solubility enhancer, as a drug carrier. The data revealed that the oral bioavailability of edaravone in rats was enhanced by tenfold using the drug carrier as compared with the edaravone suspension in 0.5% sodium carboxymethylcellulose [50]. In another study, Jin et al. [51]

showed that intravenous edaravone, when formulated as agonistic micelles using amphiphilic copolymer methoxy-poly (ethylene glycol)-*b*-poly (D,L-lactic acid) (PEG-PLA) in ischemic mice, resulted in approximately eightfold higher brain levels than naïve edaravone, suggesting that further lipophilic formulation of edaravone would facilitate more uptake into the brain [51]. Overall, based on the comparative preclinical brain penetration data discussed earlier, it could be deduced that brain distribution of edaravone does not appear to be overtly influenced by efflux capacity at the BBB, unlike riluzole.

The metabolism of riluzole is very complex and undergoes phase I and II metabolism. Furthermore, being an oral therapy it makes the drug more susceptible to presystemic metabolism. As genetic polymorphism (i.e., *CYP1A2*) plays a key role in modulating the expression and activity of the metabolic enzymes, the occurrence of high inter-subject variation with riluzole therapy could be amply justified. It should also be noted that CYP1A2 is an inducible enzyme, as observed in smokers and/or with coadministration of drugs in this patient population (i.e., corticosteroids) or patients exposed to other environmental chemicals such as polycyclic aromatic hydrocarbon (PAH) compounds that represent a class of ubiquitous environmental chemicals [52–54]. On the other hand, the metabolic disposition of edaravone appears somewhat simpler since it only undergoes glucuronide conjugation. Although a polymorphic form of UGT (i.e., UGT1A1, a minor contributor) is involved, it is less likely to play a major part in the elimination of edaravone dominated by other non-polymorphic UGTs. Because edaravone is an intravenous therapeutic, it may be less likely to exhibit higher inter-subject variation in terms of its efficacy. However, it is important to point out that the current approval of edaravone is restricted to such ALS patients that did not manifest an advanced stage of the disease and the effect size of the outcome in this population was small.

Based on the clinical trials, it has been suggested that edaravone was effective in treating ALS patients when combined with riluzole [55]. However, such a combination therapy utilizing edaravone and riluzole should be considered earlier in treatment [55]. While the rationalization of the combination has not been stated, it may be speculated that the two drugs could provide some different brain distribution dynamics by the virtue of one being oral and the other being intravenous. From a pharmacokinetic perspective, the combination of the two agents is not expected to show any drug–drug interaction potential. Although UGT1A1 mediates the metabolism of both riluzole and edaravone, the potential drug–drug interaction is limited because the majority of edaravone metabolism occurs via UGT1A9 with little contribution of UGT1A1 [32].

The first key question to explore would be: is there a difference in the scavenging ability of the free radicals between the two drugs? In this regard, the free radical scavenging potential of both the drugs was not measured and reported using common animal models. However, if one considers efficacy using the surrogate marker malondialdehyde (MDA) as a common endpoint, both riluzole and edaravone reduced the MDA levels by approximately 40% in a sepsis-induced brain-injured rats and streptozotocin-induced neuronal damage model in rats, respectively [56, 57]. Based on data from this one endpoint, it would be difficult to interpret the head-to-head comparability between the two drugs since the study design employed in this animal study was different for the two drugs. Riluzole was administered subcutaneously twice daily at 6 mg/kg dose, while edaravone was dosed via the intraperitoneal route twice daily at a 9 mg/kg dose [56, 57]. In addition, it appeared that MDA level measurements were carried out on different timeframes post-dosing for both drugs. Although a clinical trial has been registered to establish a comparative efficacy and safety of riluzole versus edaravone in an Iranian ALS patient population, the study has not been initiated [58].

The second question to explore would be: will riluzole be effective as an intravenous therapy for ALS treatment? Since riluzole was shown to have absolute bioavailability of 60% with rapid absorption, intravenous administration may not provide significant benefit from a pharmacokinetic perspective. We have compared the single-dose intravenous pharmacokinetic profile of riluzole (50 mg) versus edaravone (60 mg) (Table 3). Based on the data, it could be concluded that the tenfold higher plasma exposure (AUC levels) for edaravone than riluzole was attributable to differences in systemic clearance of the two drugs. Overall, it appears that intravenous riluzole may not show additional pharmacokinetic benefits over the currently available oral therapy.

The third question would be: is it possible to have edaravone developed into an oral dosage form? As compared with riluzole, edaravone exhibited 3.7-fold higher V_d and almost ninefold lower clearance (Table 3). Furthermore, the lack of any impact of presystemic metabolism would ensure that edaravone will have a predictable pharmacokinetics. All these data indicate that there is substantial scope for the development of edaravone as an oral therapeutic. In this regard, a preclinical study showed that the bioavailability of edaravone was 100% following oral administration of edaravone from edaravone/hydroxypropyl-β-cyclodextrin complex solution including l-cysteine and sodium hydrogen sulphite [59]. From the edaravone oral dosage form development perspective, it was suggested that solubility and stability are the major roadblocks along with the need for an acidic environment

Table 3 Key pharmacokinetic parameters of riluzole versus edaravone

Pharmacokinetic parameters	Riluzole (50 mg IV) [33]	Edaravone (60 mg IV) [28, 34]
C_{max} (μg/mL)	0.58 ± 0.14	4.54 ± 0.90
C_τ (μg/mL)[a]	0.05[b]	0.77 ± 0.35
$t_{½}$ (h)	5.9 ± 2.1	2.57 ± 0.32
AUC (μg·h/mL)	1.08 ± 0.20	11.59 ± 3.62
CL/*F* (L/h)	47.64 ± 8.4	5.4 ± 1.8
V_d (L/kg)	5.65 ± 2.17	20.7 ± 6.5
Plasma protein binding (%) [23, 36]	96	92

Data expressed as mean ± SD, unless indicated otherwise

AUC area under the plasma concentration–time curve, *CL/F* total body clearance, C_{max} maximum plasma concentration, *IV* intravenous, *SD* standard deviation, $t_{½}$ half-life, V_d volume of distribution

[a]Steady-state concentration measured on Day 7 for riluzole (after oral dosing) and Day 14 for edaravone (after intravenous dosing)

[b]No SD reported

and protection against oxidative degradation [60]. Therefore, Parikh et al. [60] developed a novel formulation using a mixture of labrasol (as surfectant) and an acidic aqueous system; the resulting formulation was found to be stable at ≤ 40 °C for at least 1 month. Furthermore, an oral pharmacokinetic study in rats showed 5.7-fold higher relative bioavailability of edaravone with the novel oral formulation than the edaravone suspension in 0.5% sodium carboxymethylcellulose [60]. In another study, the same group of authors investigated the potential implication of lipid-based nanosystems for developing a suitable oral dosage form for edaravone. The findings demonstrated a nine- and 11-fold enhancement in oral bioavailability of edaravone when administered as solid lipid-based nanosystems and liquid lipid-based nanosystems, respectively, in rats compared with edaravone suspension [61]. Hence, the strategy for the clinical development of edaravone as oral therapy may be considered for better patient compliance.

9 Conclusions

The recent approval of edaravone ends the long drought in the quest for newer therapeutic approval in ALS spanning more than 20 years following the first approval of riluzole. The two approved agents provide an opportunity to treat ALS as an oral option (riluzole) or an intravenous dosing option (edaravone). The clinical pharmacokinetics of riluzole have shown more inter-subject variability relative to that of edaravone, presumably due to the occurrence of presystemic metabolism and the role of polymorphic CYP enzymes. On different comparison parameters, including intravenous pharmacokinetics, it appeared that edaravone may have an edge over riluzole in attaining the required systemic and possibly brain concentrations for effectiveness in ALS patients. However, no head-to-head clinical trial of the two agents has been performed. Some conjecture regarding the likely success of intravenous riluzole suggested that it was unlikely to be better than oral riluzole given its fast systemic clearance; on the contrary, there appeared to be scope for oral dosage form development of edaravone. Based on the current knowledge of the existence of pharmaco-resistance at the BBB in ALS patients, there may be opportunities to further optimize the therapy with the selection of the right agents for combination that may facilitate better brain penetration of edaravone and riluzole. The suggestion that combination of edaravone and riluzole may produce a better outcome in ALS patients showed that there may be an opportunity for dose optimization of the two agents with P-gp efflux blocking drug(s) at the BBB.

Compliance with Ethical Standards

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Conflict of interest Ranjeet P. Dash, R. Jayachandra Babu and Nuggehally R. Srinivashave declare no conflicts of interest or competing interests relevant to the content of this review article.

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